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Washington, D.C. 20231

**NEW UTILITY PATENT APPLICATION TRANSMITTAL**

Sir:

Transmitted herewith for filing is a new utility patent application, identifiable by Attorney Docket Number 5/891-1-C1 Reissue, of the following inventor(s),

Wolfgang Grell, Rudolf Hurnaus, Robert Sauter, Manfred Reiffen and Eckhard Rupprecht

entitled:

PHENYLACETIC ACID BENZYLAMIDES

comprising the following elements:

- ☒ specification (description, claims and abstract) comprising 145 pages  
☐ pages of drawings  
☒ other: Reissue Application Declaration by the Assignee, Reissue Application by the Assignee, Offer to Surrender Patent and Certified Copy of Certificate of Title

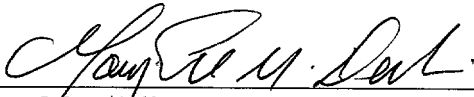
☐ This application is being filed on behalf of the above named inventor(s) by the undersigned, pursuant to 37 CFR 1.41(c). Consequently, an oath or declaration under 37 CFR 1.63 is not enclosed but will be submitted at a later date.

The fee due for the filing of this application has been calculated as shown below:

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FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
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INDEPENDENT CLAIMS	1 - 3=	0	x \$80.00	\$0.00
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BASIC FEE				\$790.00
TOTAL FILING FEE				\$790.00

Charge Deposit Account No. 02-2955 in the amount of \$ 790.00. The Commissioner is further authorized to charge any additional filing fees required under 37 CFR 1.16 and any patent application processing fees under 37 CFR 1.17, or credit any overpayment, to Deposit Account No. 02-2955. Duplicate copies of this form are enclosed.

Date: October 7, 1997



Mary-ellen M. Devlin  
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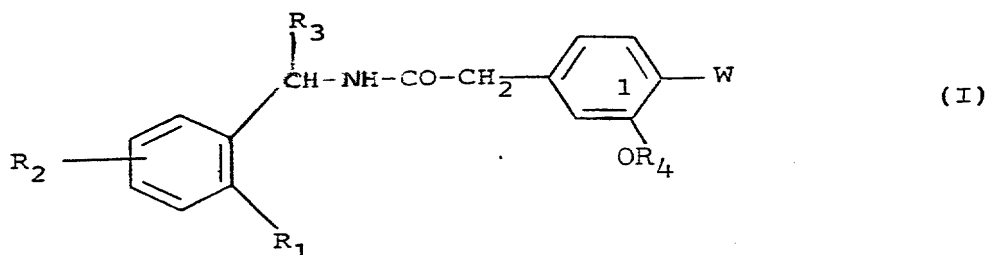
By: Mary-ellen M. Devlin  
Date: October 7, 1997

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PHENYLACETIC ACID BENZYLAMIDES

This invention relates to novel phenylacetic acid benzylamides and their non-toxic salts, to methods of preparing these compounds, to pharmaceutical compositions containing them as active ingredients, and to a method of using them as hypoglycemics.

More particularly, the present invention relates to a novel class of compounds represented by the formula



wherein

$R_1$  represents an unbranched alkyleneimino group with 4 to 6 carbon atoms optionally mono- or di-(alkyl of 1 to 3 carbon atoms)-substituted;

$R_2$  represents a hydrogen or halogen atom or a methyl or methoxy group;

$R_3$  represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy, alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain from 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 or 3 car-

bon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms;

$R_4$  represents a hydrogen atom, a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxyl, alkoxycarbonyl, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethenyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group; and

when  $R_3$  is other than hydrogen and/or the radical  $R_1$  contains an optically active carbon atom, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the  $R_1$ -position.

Specific embodiments of substituents  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and W are the following:

10  $R_1$ : Pyrrolidino, piperidino, hexamethyleneimino, methyl-pyrrolidino, dimethyl-pyrrolidino, ethyl-pyrrolidino, 2-methyl-piperidino, 3-methyl-piperidino, 4-methyl-piperidino, 3,3-dimethyl-piperidino, cis-3,5-dimethyl-piperidino, trans-3,5-dimethyl-piperidino, ethyl-piperidino, diethyl-piperidino, 15 methyl-ethyl-piperidino, propyl-piperidino, methyl-propyl-piperidino or isopropyl-piperidino.

$R_2$ : Hydrogen, fluorine, chlorine, bromine, methyl or methoxy.

R<sub>3</sub>: Hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, 2-methyl-n-butyl, 3-methyl-n-butyl, 2,2-dimethyl-propyl-n-hexyl, 4-methyl-n-pentyl, n-heptyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, methylphenyl, methoxyphenyl, 1-propen-1-yl, 2-methyl-1-propen-1-yl, 3-methyl-2-buten-2-yl, 2-propen-1-yl, 2-methyl-2-propen-1-yl, 2-buten-1-yl, 2-methyl-2-buten-1-yl, 3-methyl-2-buten-1-yl, 3-buten-1-yl, 2-methyl-3-buten-1-yl, 3-methyl-3-buten-1-yl, 2-hexen-1-yl, 1-propyn-1-yl, 2-propyn-1-yl, 2-butyn-1-yl, 2-pentyn-1-yl, hydroxymethyl, 1-hydroxy-ethyl, 2-hydroxy-ethyl, methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, 1-methoxy-ethyl, 2-methoxy-ethyl, 1-ethoxy-ethyl, 2-ethoxy-ethyl, 2-n-propoxy-ethyl, 2-isopropoxy-ethyl, acetoxymethyl, propionyloxymethyl, 1-acetoxy-ethyl, 2-acetoxy-ethyl, 1-propionyloxy-ethyl, 2-propionyloxy ethyl, tetrahydrofuran-2-yl-methyl, 2-(tetrahydrofuran-2-yl)-ethyl, tetrahydrofuran-3-yl-methyl, tetrahydropyran-2-yl-methyl, 2-(tetrahydropyran-2-yl)-ethyl, tetrahydropyran-3-yl-methyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 2-cyclopropyl-ethyl, 2-cyclobutyl-ethyl, 2-cyclopentyl-ethyl, 2-cyclohexyl-ethyl, 2-cycloheptyl-ethyl, benzyl, 1-phenyl-ethyl, 2-phenyl-ethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec.butoxycarbonyl, isobutoxycarbonyl or tert.butoxycarbonyl.

R<sub>4</sub>: Hydrogen, methyl, ethyl, n-propyl, isopropyl, allyl.

W: Methyl, hydroxymethyl, formyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec.butoxycarbonyl, isobutoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl, 3-phenylpropoxycarbonyl,

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cyanomethyl, 2-cyano-ethyl, 2-cyano-ethenyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, n-propoxycarbonylmethyl, n-butoxycarbonylmethyl, tert.butoxycarbonylmethyl, 2-methoxycarbonyl-ethyl, 2-ethoxycarbonyl-ethyl, 2-n-propoxycarbonyl-ethyl, 2-isopropoxycarbonyl-ethyl, 2-n-butoxycarbonyl-ethyl, 2-tert.butoxycarbonyl-ethyl, 2-methoxycarbonyl-ethenyl, 2-ethoxycarbonyl-ethenyl, 2-n-propoxycarbonyl-ethenyl or 2-tert.butoxycarbonylethenyl.

One subgeneric aspect is constituted by those compounds of the formula I wherein

R<sub>1</sub> represents a pyrrolidino, piperidino, 4-methyl-piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneimino group;

R<sub>2</sub> represents a hydrogen, fluorine or chlorine atom;

R<sub>3</sub> represents hydrogen atom, an alkyl group with 1 to 6 carbon atoms, a phenyl, methyl-phenyl, chloro-phenyl, methoxy-phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, tetrahydrofuran-2-yl-methyl, tetrahydropyran-2-yl-methyl, propargyl, hydroxymethyl, ethoxymethyl, acetoxymethyl, propionyloxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl group or a branched or unbranched alkenyl group with 3 or 4 carbon atoms;

R<sub>4</sub> represents a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxyl, benzyloxycarbonyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, cyanomethyl, 2-carboxy-ethyl, 2-ethoxycarbonyl-ethyl, 2-cyano-ethyl, 2-carboxy-ethenyl, 2-ethoxycarbonyl-ethenyl or 2-cyano-ethenyl group or an alkoxy-carbonyl group with 1 to 4 carbon atoms in the alkoxy part; and

when  $R_3$  is other than hydrogen and/or  $R_1$  represents the 3-methyl-piperidino group, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the  $R_1$ -position.

A preferred sugenus is constituted by those compounds of the formula I wherein

$R_1$  represents a piperidino group;

$R_2$  represents a hydrogen atom;

$R_3$  represents an alkyl group with 1 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, tetrahydropyran-2-yl-methyl, cyclopropylmethyl or cyclohexylmethyl group;

$R_4$  represents a methyl, ethyl or allyl group; and

W represents a carboxyl, methoxycarbonyl, ethoxycarbonyl or cyanomethyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

An especially preferred subgenus is constituted by those compounds of the formula I wherein

$R_1$  represents a piperidino group;

$R_2$  represents a hydrogen atom;

R<sub>3</sub> represents an alkyl group with 3 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, cyclopropylmethyl or cyclohexylmethyl group;

R<sub>4</sub> represents a methyl or ethyl group; and

W represents a carboxyl group;

especially those compounds of the before mentioned preferred subgenus, wherein

R<sub>3</sub> represents an alkyl group with 3 to 6 carbon atoms, a 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

A preferred subgenus of the before mentioned compounds are those, wherein

R<sub>3</sub> represents a n-propyl, n-butyl, isobutyl, sec.butyl, n-pentyl, 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group, especially when

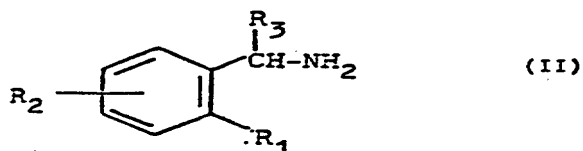
R<sub>3</sub> represents a n-propyl, n-butyl, isobutyl, sec.butyl or n-pentyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.



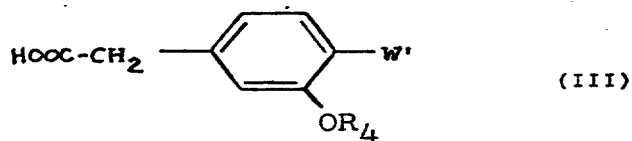
According to the invention, the new compounds are obtained by the following methods:

a) reacting an amine of formula



wherein

R<sub>1</sub> to R<sub>3</sub> are defined as hereinbefore, with a carboxylic acid of formula



wherein

R<sub>4</sub> is defined as hereinbefore and W' has the meanings given for W hereinbefore, in which any carboxy group contained in the group W can be protected by a protecting group, or with the reactive derivatives thereof optionally prepared in the reaction mixture, if necessary with subsequent splitting off of any protecting group used.

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Examples of reactive derivatives of a compound of formula III which can be used include the esters thereof, such as the methyl, ethyl or benzyl esters, the thioesters such as the methylthio or ethylthioesters, the halides such as the acid chloride, the anhydrides or imidazolides thereof.

The reaction is appropriately carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethyl formamide, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide,

N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyl-diimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which can simultaneously be used as solvent, at temperatures of between -25°C and 250°C, but preferably at temperatures of between -10°C and the boiling temperature of the solvent used. The reaction can also be carried out without a solvent and furthermore any water formed during the reaction can be removed by azeotropic distillation, e.g. by heating with toluene using a water separator, or by adding a drying agent such as magnesium sulphate or a molecular sieve.

If necessary, the subsequent splitting off of a protecting group is preferably carried out by hydrolysis, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or

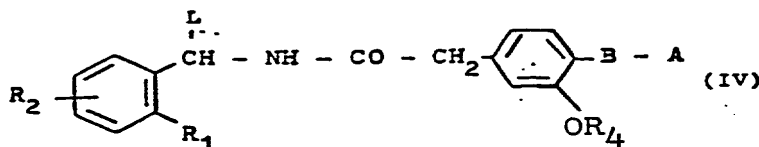
trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between -10 and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

A tert.butyl group used as protecting group can also be split off thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic acid, sulphuric, phosphoric or polyphosphoric acid.

Furthermore, a benzyl group used as protecting group can also be split off hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide.

b) In order to prepare compounds of formula I wherein  $R_3$  represents a carboxy or alkoxycarbonyl group and W has the meanings given hereinbefore or W represents a carboxy, carboxymethyl, 2-carboxy-ethyl, 2-carboxy-ethenyl, alkoxycarbonyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group and  $R_3$  has the meanings given hereinbefore:

Hydrolysis, thermolysis, hydrogenolysis or alcoholysis of a compound of formula



wherein

$\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_4$  are as hereinbefore defined,

B represents a bond, a methylene, ethylene or ethenylene group,

A and L each represent a nitrile group or a group which can be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis and

L additionally has the meanings given for  $\text{R}_3$  hereinbefore.

Examples of hydrolysable groups include functional derivatives of the carboxy group and the unsubstituted or substituted amides, esters, thioesters, ortho esters, iminoethers, amidines or anhydrides thereof, the nitrile group, the tetrazolyl group, an optionally substituted 1,3-oxazol-2-yl or 1,3-oxazolin-2-yl group,

examples of thermolytically cleavable groups include esters with tertiary alcohols, e.g. the tert.butyl ester,

examples of hydrogenolytically cleavable groups include aralkyl groups, e.g. the benzyl group, and

examples of alcoholytically cleavable groups include the cyano group.

The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or

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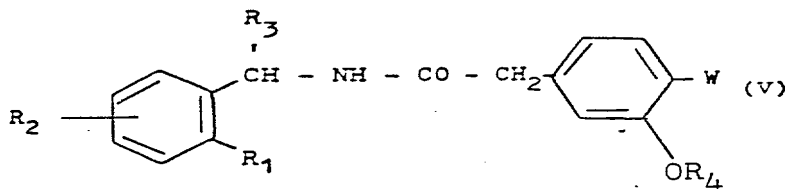
in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between -10 and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture, and the alcoholysis of a cyano group is preferably effected in an excess of the corresponding alcohol such as methanol, ethanol or propanol and in the presence of an acid such as hydrochloric acid at elevated temperatures, e.g. at the boiling temperature of the reaction mixture.

If A and/or L in a compound of formula IV represents a nitrile or aminocarbonyl group, these groups can be converted into a corresponding carboxy compound by means of 100% phosphoric acid at temperatures of between 100 and 180°C, preferably at temperatures of between 120 and 160°C, or with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, the latter conveniently being used as solvent as well, at temperatures of between 0 and 50°C.

If A and/or L in a compound of formula IV represents the tert.butyloxycarbonyl group for example, the tert.butyl group can also be split off thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic, sulphuric, phosphoric or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures of between 40 and 100°C.

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Splitting off a protecting group from a compound of formula



R<sub>1</sub> to R<sub>3</sub> and W are as hereinbefore defined and R<sub>5</sub> represents a protecting group for a hydroxy group.

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trimethylsilyl group.

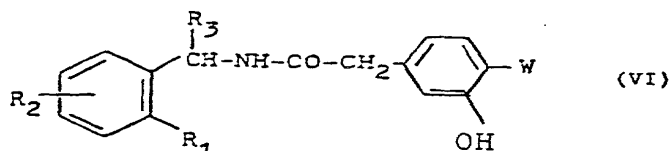
Depending on the protecting group used, the protecting groups mentioned above can be split off either by hydrolysis or by hydrogenolysis, optionally in a suitable solvent, at temperatures of between -78 and 250°C.

For example, ether splitting is carried out in the presence of an acid such as hydrochloric, hydrobromic or sulphuric acid, boron tribromide, aluminium trichloride or pyridine hydrochloride, conveniently in a suitable solvent such as methylene chloride, glacial acetic acid or water or in mixtures thereof at temperatures of between -78 and 250°C. The ether splitting is carried out in the presence of a proton acid conveniently at temperatures of between 0 and 150°C, preferably at temperatures of between 50 and 150°C or with a Lewis acid preferably in a solvent such as a chloride at temperatures of between

For example, any protecting group used such as a benzyl group can be split off hydrogenolytically with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide, preferably at ambient temperature, for example, and under a hydrogen pressure of from 1 to 5 bar.

d) In order to prepare compounds of formula I wherein  $R_4$  represents methyl, ethyl or allyl group:

Reacting a compound of formula



wherein

$\text{R}_1$  to  $\text{R}_3$  and  $\text{W}$  are as hereinbefore defined, with a compound of formula



wherein

$\text{R}_6$  represents methyl, ethyl or allyl group

$\text{X}$  represents a nucleophilically exchangeable group such as a halogen atom, a sulphonyloxy group or, together with the adjacent hydrogen atom, a diazo group, if  $\text{R}_6$  represents an alkyl group with 1 to 3 carbon atoms, if necessary with subsequent hydrolysis.

The reaction is conveniently carried out with a corresponding halide, sulphonic acid ester, sulphuric acid diester or diazoalkane, e.g. with methyl iodide, dimethyl sulphate, ethyl bromide, diethyl sulphate, ~~propyl bromide, isopropyl bromide~~, allyl bromide, ethyl p-toluenesulphonate, ~~isopropylmethanesulphonate~~ or diazomethane, optionally in the presence of a base such as sodium hydride, potassium carbonate, sodium hydroxide, potassium tert.butoxide or triethylamine in a suitable solvent such as acetone, diethylether, tetrahydrofuran, dioxan or dimethylformamide at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C.

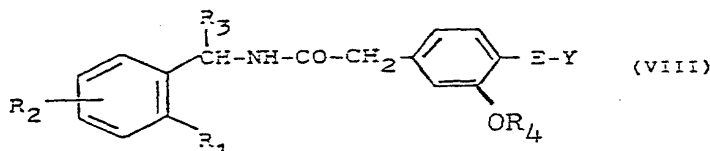


If in a compound of formula VI  $R_3$  represents a carboxy group and/or W represents a carboxy, carboxymethyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group, this compound can simultaneously be converted into the corresponding ester compound. A compound thus obtained is, if necessary by cleaving the ester group, converted into the desired compound of formula I.

The cleaving of the ester group is carried out hydrolytically, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between  $-10$  and  $120^\circ\text{C}$ , e.g. at temperatures of between ambient temperature and the boiling point of the reaction mixture.

e) In order to prepare compounds of formula I wherein W represents a cyanomethyl or 2-cyano-ethyl group:

Reacting a compound of formula



wherein

$R_1$  to  $R_4$  are as hereinbefore defined,

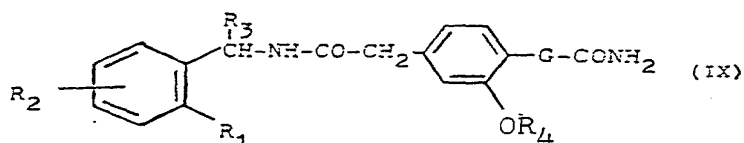
E represents a methylene or ethylene group and

Y represents a nucleophilically exchangeable group such as a halogen atom or a sulphonyloxy group, e.g. a chlorine, bromine or iodine atom or a methane-sulphonyloxy or p-toluenesulphonyloxy group, with an alkali metal cyanide such as sodium or potassium cyanide.

The reaction is conveniently carried out in a suitable solvent such as dimethylsulphoxide or dimethylformamide at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C, or in a two-phase system such as methylene chloride/water in the presence of a phase transfer catalyst such as benzyl-tributyl-ammonium chloride at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C.

f) In order to prepare compounds of formula I wherein W represents a cyanomethyl, 2-cyano-ethyl or 2-cyano-ethenyl group:

Dehydration of a compound of formula



wherein

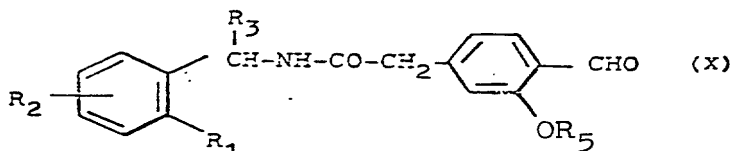
R<sub>1</sub> to R<sub>4</sub> are as hereinbefore defined and G represents a methylene, ethylene or ethenylene group.

The dehydration is carried out with a water-cleaving agent such as phosphorus pentoxide, phosphorus oxychloride,

triphenylphosphine/carbon tetrachloride or p-toluene-sulphonic acid chloride, optionally in a solvent such as methylene chloride, acetonitrile or pyridine at temperatures of between 0 and 100°C, preferably at temperatures of between 20°C and 80°C.

g) In order to prepare compounds of formula I wherein W represents a 2-cyano-ethenyl, 2-carboxy-ethenyl or 2-alkoxycarbonyl-ethenyl group:

Reacting a compound of formula



wherein

R<sub>1</sub> to R<sub>4</sub> are as hereinbefore defined, with a corresponding acetic acid derivative of formula



wherein Q represents a carboxy, alkoxycarbonyl or cyano group and

Z represents a hydrogen atom, an alkoxycarbonyl, dialkylphosphono or triphenylphosphonium halide group, optionally with subsequent hydrolysis and/or decarboxylation.

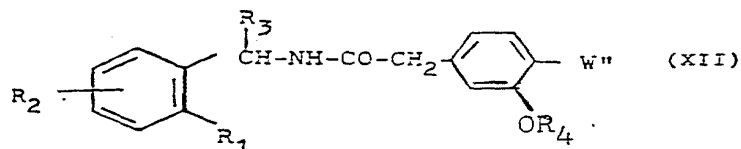
The reaction is conveniently carried out in a solvent such as diethylether, tetrahydrofuran, 1,2-dimethoxyethane, dioxan, dimethylformamide, toluene or pyridine in the presence of a base as condensation agent such as sodium carbonate, sodium hydride, potassium

tert.butoxide or piperidine at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 80°C.

The subsequent hydrolysis and/or decarboxylation is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between -10°C and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

h) In order to prepare compounds of formula I wherein W represents a 2-carboxy-ethyl, 2-alkoxy-carbonyl-ethyl or 2-cyano-ethyl group:

Reduction of a compound of formula



wherein

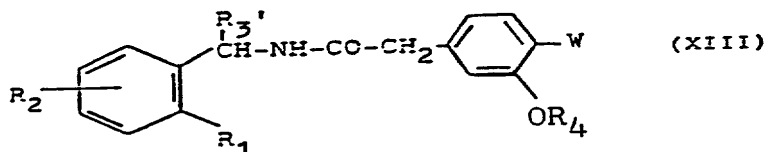
R<sub>1</sub> to R<sub>4</sub> are as hereinbefore defined and W'' represents a 2-carboxy-ethenyl, 2-alkoxycarbonyl-ethenyl or 2-cyano-ethenyl group.

The reduction is preferably carried out in a suitable solvent such as methanol, ethanol, isopropanol, ethyl acetate, dioxan, tetrahydrofuran, dimethylformamide, benzene or benzene/ethanol with hydrogen in the

presence of a suitable hydrogenation catalyst such as palladium/charcoal, Raney nickel or tris-[triphenylphosphine]-rhodium(I)chloride at temperatures of between 0 and 100°C, but preferably at temperatures of between 20°C and 50°C, under a hydrogen pressure of from 1 to 5 bar or, if W<sup>+</sup> contains a cyano group, with nascent hydrogen, e.g. with magnesium/methanol, or with a copper hydride complex, e.g. with the complex prepared from copper bromide, sodium bis(2-methoxyethoxy)-aluminium hydride and sec.butanol, at temperatures of between -78 and 50°C. Other groups can be reduced at the same time, e.g. a benzyloxy group can be reduced to the hydroxy group, an alkenyl or alkynyl group can be reduced to the corresponding alkyl group or a formyl group can be reduced to the hydroxymethyl group, or they can be replaced by hydrogen atoms, e.g. a halogen atom can be replaced by a hydrogen atom.

i) In order to prepare compounds of formula I wherein R<sub>3</sub> represents an alkyl group with 1 or 2 carbon atoms substituted by an alkoxy or alkanoyloxy group:

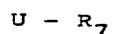
Reacting a compound of formula



wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub> and W are as hereinbefore defined and R<sub>3</sub>' represents an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy group,

with a compound of formula



(XIV)

wherein

$R_7$  represents an alkyl group with 1 to 3 carbon atoms or an acetyl or propionyl group and U represents a nucleophilically exchangeable group such as a halogen atom, a sulphonyloxy group, an acetoxy or propionyloxy group or, together with the adjacent hydrogen atom, represents a diazo group if  $R_7$  represents an alkyl group with 1 to 3 carbon atoms, optionally with subsequent hydrolysis.

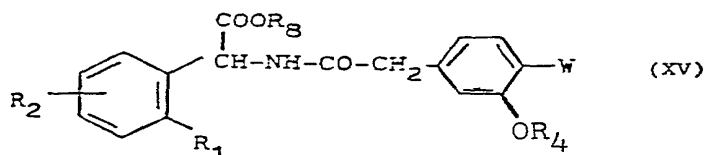
The reaction is conveniently carried out with a corresponding halide, anhydride, sulphonic acid ester, sulphuric acid diester or diazoalkane, e.g. with methyl iodide, dimethyl sulphate, ethyl iodide, diethyl sulphate, n-propyl iodide, isopropyl bromide, acetyl chloride, acetic hydride, propionic acid chloride, propionic acid anhydride, ethyl p-toluene-sulphonate or isopropylmethanesulphonate, optionally in the presence of a base such as sodium hydride, potassium carbonate, sodium hydroxide, potassium tert.butoxide or triethylamine, or with diazomethane, optionally in the presence of a Lewis acid, e.g. boron trifluoride, preferably in a suitable solvent such as acetone, diethylether, tetrahydrofuran, dioxan, pyridine or dimethylformamide at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C, in which an anhydride used as the acylating agent can simultaneously also be used as solvent.

If in a compound of formula XIII W represents a carboxy, carboxymethyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group and/or  $R_4$  represents a hydrogen

atom, this can simultaneously be converted into the corresponding ester and/or ether compound.

k) In order to prepare compounds of formula I wherein  $R_3$  represents an alkoxy carbonyl group:

Reacting a compound of formula



wherein

$R_1$ ,  $R_2$ ,  $R_4$  and W are as hereinbefore defined and  $R_3$  represents a hydrogen atom or alkali metal atom, or the reactive derivatives thereof optionally prepared in the reaction mixture, with a compound of formula



wherein

$R_9$  represents an alkyl group with 1 to 4 carbon atoms and T represents a hydroxy group or a nucleophilically exchangeable group such as a halogen atom or a sulphonyloxy group, or together with the adjacent hydrogen atom of the group  $R_9$  represents a diazo group, optionally followed by hydrogenolysis if W contains a benzyloxycarbonyl group.

An example of a reactive derivative of a compound of formula XV is the imidazolid thereof.

The reaction is conveniently carried out in the corresponding alcohol as solvent or in a suitable solvent such as methylene chloride, chloroform, ether, tetrahydrofuran, dioxan, dimethylformamide, benzene or toluene, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of hydrogen chloride, sulphuric acid, ethyl chloroformate, thionylchloride, carbon tetrachloride/triphenylphosphine, carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide or the isourea ethers thereof, optionally in the presence of a reaction accelerator such as copper chloride and optionally in the presence of an inorganic base such as potassium carbonate or a tertiary organic base such as triethylamine, 1,8-diazabicyclo[5.4.0]-undec-7-ene or pyridine, or by transesterification, e.g. with a corresponding carbonic acid diester, at temperatures of between -20°C and 100°C, but preferably at temperatures of between -10°C and the boiling temperature of the solvent used.

The optional subsequent hydrogenolysis is carried out in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide.

If W in a compound of formula XV contains a carboxy group, this can be converted during the reaction into the corresponding alkoxycarbonyl group.

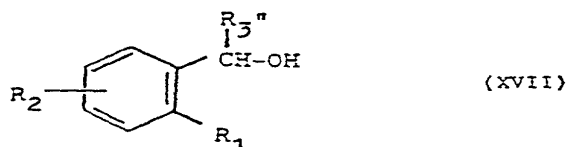
1) In order to prepare compounds of formula I wherein

$R_4$  represents a hydrogen atom, methyl, ethyl or allyl group and



W represents a methyl, formyl, carboxy, carboxymethyl, 2-carboxy-ethyl, alkoxycarbonyl, alkoxycarbonylmethyl or 2-alkoxycarbonylethyl group, in which the alkoxy part can contain from 1 to 4 carbon atoms.

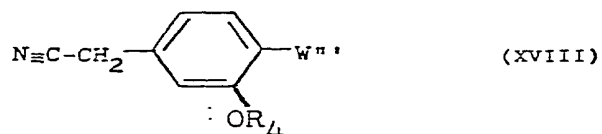
Reacting a compound of formula



wherein

$R_1$  and  $R_2$  are as hereinbefore defined and

$R_3$  represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by an alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, wherein the alkoxy part can contain 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 or 3 carbon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms, with a compound of formula



wherein

$\text{R}_4$  is as hereinbefore defined and

$\text{W}'''$  represents a methyl, formyl, carboxy, carboxymethyl, 2-carboxy-ethyl, alkoxycarbonyl, alkoxy-carbonylmethyl or 2-alkoxy-carbonyl-ethyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms.

The reaction is carried out in the presence of a strong acid which can simultaneously serve as solvent, preferably in concentrated sulfuric acid, at temperatures of between 0 and 150°C, preferably at temperatures of between 20 and 100°C.

If in a compound of formula XVIII  $\text{R}_4$  represents an allyl group, this is split off during the reaction or after the reaction by the addition of water.

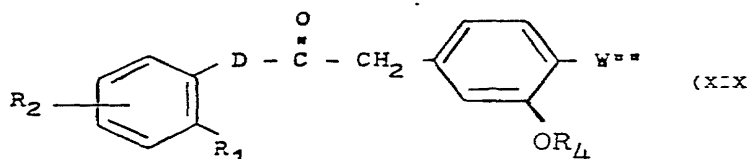
m) In order to prepare compounds of formula I wherein

$\text{R}_4$  represents a hydrogen atom, a methyl or ethyl group,

$\text{R}_3$  represents an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by an alkoxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group in which the alkoxy part can contain 1 to 3 carbon atoms and the cycloalkyl part can contain 5 to 7 carbon atoms, and

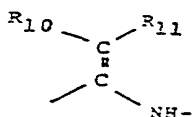
W represents a methyl, hydroxymethyl, carboxy, cyanomethyl, 2-cyano-ethyl, carboxymethyl, 2-carboxy-ethyl, alkoxy-carbonyl, alkoxy-carbonyl-methyl or 2-alkoxy-carbonyl-ethyl group in which the alkoxy part can contain from 1 to 4 carbon atoms.

Reduction of a compound of formula

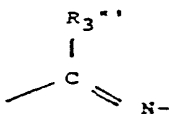


wherein

$\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_4$  are as hereinbefore defined and D represents a group of formula



or



in which  $\text{R}_3'''$  represents a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group.

$\text{R}_{10}$  and  $\text{R}_{11}$  together with the carbon atom between

them represent an alkylidene group with 1 to 7 carbon atoms, an alkylidene group with 1 or 2 carbon atoms substituted by an alkoxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain 1 to 3 carbon atoms and the cycloalkyl part can contain 5 to 7 carbon atoms, and

W'' represents a methyl, hydroxymethyl, formyl, carboxy, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethyl, carboxymethyl, 2-carboxy-ethyl, 2-carboxy-ethenyl, alkoxycarbonyl, alkoxy-carbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group, in which the alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group.

The reduction is preferably carried out with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal or Raney-nickel in a suitable solvent such as methanol, ethanol, isopropanol, ethyl acetate, dioxan, tetrahydrofuran, dimethylformamide, benzene or benzene/ethanol at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 50°C, and under a hydrogen pressure of from 1 to 5 bar. When a suitable chiral hydrogenation catalyst is used, such as a metal ligand complex e.g. [(2S),(4S)-1-tert.butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine-rhodium-cyclo-octadiene(1,5)]-perchlorate, the addition of hydrogen occurs enantioselectively. Moreover, in the catalytic hydrogenation, other groups can also be reduced, e.g. a benzyloxy group can be reduced to the hydroxy group or a formyl group can be reduced to the hydroxy methyl group, or they can be replaced by hydrogen atoms, e.g. a halogen atom can be replaced by a hydrogen atom.

5 If a compound of the formula I is obtained wherein  $R_2$  is halogen and/or  $R_3$  is halophenyl and/or W is hydroxymethyl which has been converted into halomethyl, it may, if desired, be converted by de-halogenation into a corresponding compound of the formula I wherein  $R_2$  is hydrogen and/or  $R_3$  is phenyl and/or W is methyl.

10 If a compound of the formula I is obtained wherein W is carboxyl, this compound may, if desired, be converted by esterification into a corresponding compound of the formula I wherein W is alkoxycarbonyl or phenylalkoxycarbonyl.

15 If a compound of the formula I is obtained wherein W is carboxyl, alkoxycarbonyl or phenylalkoxycarbonyl, this compound may be converted by reduction into a corresponding compound of the formula I wherein W is formyl or hydroxymethyl.

20 If a compound of the formula I is obtained wherein W is hydroxymethyl, this compound may be converted by oxidation into a corresponding compound of the formula I wherein W is formyl or carboxyl.

25 If a compound of the formula I is obtained wherein W is carboxyl, this compound may be converted, via a sulfonic acid hydrazide and subsequent disproportionation, into a corresponding compound of the formula I wherein W is formyl.

5           The subsequent dehalogenation is advantageously carried  
out by catalytic hydrogenation, for example with palladium-on-  
charcoal, in a suitable solvent such as methanol, ethanol,  
tetrahydrofuran, dioxane, dimethylformamide or ethyl acetate,  
optionally in the presence of a base such as triethylamine, and  
10       at temperatures between 20° and 100°C, preferably at 20° to 50°C.

          The subsequent esterification is advantageously carried  
out in a suitable solvent, for instance in a corresponding  
alcohol, pyridine, toluene, methylene chloride, tetrahydrofuran  
or dioxane, in the presence of an acid-activating and/or de-  
15       hydrating agent such as thionyl chloride, ethyl chloroformate,  
carbonyldiimidazole or N,N'-dicyclohexylcarbodiimide or the  
isourea ethers thereof, optionally in the presence of a reaction  
accelerator such as copper chloride, or by trans-esterification,  
for instance with a corresponding carbonic acid diester, at  
20       temperatures between 0° and 100°C, but preferably at temperatures  
between 20° and the boiling point of the solvent which is used.

          The subsequent reduction is preferably carried out with  
a metal hydride, for example with a complex metal hydride such  
as lithium aluminum hydride, lithium borohydride or lithium  
25       borohydride/trimethylborate, in a suitable solvent such as  
diethyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane  
at temperatures between 0° and 100°C, but preferably at  
temperatures between 20°C and 60°C.

          The subsequent oxidation of an alcohol is preferably

5 carried out with an oxidizing agent, for instance with pyridinium  
chlorochromate or manganese dioxide, in a suitable solvent such  
as chloroform or methylene chloride at temperatures between  
-10° and 50°C, but preferably at temperatures between 0° and  
20°C.

10 The subsequent disproportionation of a sulfonic acid  
hydrazide, obtained by reacting a corresponding hydrazine with  
a suitable reactive carboxylic acid derivative, is carried out  
in the presence of a base such as sodium carbonate in a solvent  
such as ethylene glycol at temperatures between 100°C and 200°C,  
15 but preferably at 160-170°C.

If according to the invention a racemic compound of  
formula I is obtained wherein  $R_3$  has the meanings  
given hereinbefore with the exception of the hydrogen  
atom, this compound can be resolved into the  
enantiomers thereof via the diastereomeric adducts,  
complexes, salts or derivatives thereof.

The subsequent racemate splitting is preferably  
carried out by column or HPL chromatography by  
forming diastereomeric adducts or complexes in a  
chiral phase.

The compounds of formula I obtained according to the  
invention can also be converted into the salts  
thereof and, for pharmaceutical use, into the  
nontoxic, pharmaceutically acceptable salts thereof  
with inorganic or organic acids or bases. Suitable  
acids include, for example, hydrochloric,  
hydrobromic, sulfuric, phosphoric, lactic, citric,  
tartaric, succinic, maleic, fumaric, aspartic or  
glutamic acid and suitable bases include sodium  
hydroxide, potassium hydroxide, calcium hydroxide,  
cyclohexylamine, ethanolamine, diethanolamine,  
triethanolamine, ethylenediamine, lysine or arginine.

The compounds of formulae II to XIX used as starting materials are known from the literature in some cases or can be obtained by methods known per se.

Thus, for example, a compound of formula II is obtained by reducing a corresponding nitrile with lithium aluminium hydride or with catalytically activated hydrogen, by reacting a corresponding nitrile with a corresponding grignard or lithium compound and subsequent lithium-aluminium hydride reduction or subsequent hydrolysis to form the ketimine which is subsequently reduced with catalytically activated hydrogen, with a complex metal hydride or with nascent hydrogen, by hydrolysis or by hydrazinolysis of a corresponding phthalimido compound, by reacting a corresponding ketone with ammonium formate and subsequent hydrolysis or with an ammonium salt in the presence of sodium cyanoborohydride, by reduction of a corresponding oxime with lithium aluminium hydride, with catalytically activated or nascent hydrogen, by reduction of a corresponding N-benzyl or N-1-phenylethyl Schiff's base e.g. with a complex metal hydride in ether or tetrahydrofuran at temperatures of between -78°C and the boiling temperature of the solvent used with subsequent splitting off of the benzyl or 1-phenylethyl group by catalytic hydrogenation, by lithiation of a corresponding benzylideneimino-benzyl compound, e.g. by means of lithium-diisopropylamide at temperatures of between -78 and 20°C, subsequent reaction with a corresponding halogen compound, e.g. with a corresponding bromoalkyl, bromoalkenyl or bromoalkinyl compound, and subsequent hydrolysis, by Ritter reaction of a corresponding alcohol with potassium cyanide in sulfuric acid, by Hofmann, Curtius, Lossen or Schmidt degradation of a



corresponding compound or by converting a corresponding benzaldehyde into a corresponding glycine derivative, e.g. using sodium cyanide/ammonium carbonate in ethanol/water into a corresponding hydantoin derivative, hydrolysis thereof, and, if necessary, subsequent esterification and, if necessary, subsequent reduction, e.g. with a complex metal hydride in ether or tetrahydrofuran.

An amine of formula II thus obtained having a chiral centre can be resolved into its enantiomers by racemate splitting, e.g. by fractional crystallization of the diastereomeric salts with optically active acids and subsequent decomposition of the salts or by column or HPL chromatography, optionally in the form of the acyl derivative thereof, or by forming diastereomeric compounds, separating them and subsequently splitting them.

Moreover, an optically active amine of formula II can also be prepared by enantioselective reduction of a corresponding ketimine using complex boron or aluminium hydrides in which some of the hydride hydrogen atoms have been replaced by optically active alkoxide groups, or by means of hydrogen in the presence of a suitable chiral hydrogenation catalyst or analogously starting from a corresponding N-benzyl or N-(1-phenethyl)-ketimine or from a corresponding N-acyl-ketimine or enamide and optionally subsequently splitting off the benzyl, 1-phenethyl or acyl group.

Furthermore, an optically active amine of formula II can also be prepared by diastereoselective reduction of a corresponding ketimine or hydrazone substituted at the nitrogen atom with a chiral group, using a complex or non-complex boron or aluminium hydride in

which some of the hydride hydrogens can optionally be replaced by corresponding alkoxide, phenoxide or alkyl groups or using hydrogen in the presence of a suitable hydrogenation catalyst optionally with subsequent splitting off of the chiral auxiliary group by catalytic hydrogenolysis or hydrolysis.

Moreover, an optically active amine of formula II can also be prepared by diastereo-selective addition of a corresponding organometallic compound, preferably a grignard or lithium compound, to a corresponding aldimine substituted with a chiral group at the nitrogen atom, by subsequent hydrolysis and optionally subsequent splitting off of the chiral auxiliary group by catalytic hydrogenolysis or hydrolysis.

The compounds of formulae IV, V, VI, VIII, IX, X, XII, XIII and XV used as starting materials are obtained by reacting a corresponding amine with a suitable carboxylic acid or a reactive derivative thereof and, if necessary, subsequently splitting off any protecting group used.

A compound of formula XVII used as starting material is obtained by reducing a corresponding carbonyl compound by reacting a corresponding carbonyl compound with a corresponding grignard or lithium reagent or by hydrolysis or alcoholysis of a corresponding cyanohydrin and, if necessary, subsequent esterification.

A compound of formula XIX used as starting material is obtained by acylating a corresponding ketimine or the organometallic complex thereof with a corresponding carboxylic acid or reactive derivatives thereof, optionally with tautomerization.

The following examples illustrate the present invention and will enable others skilled in the art to understand it more completely. It should be understood, however, that the invention is not limited solely to the particular examples given below.

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Example 1

Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}amino-carbonylmethyl]-benzoate

2 g (7.9 mmols) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 2.46 g (9.38 mmols) of triphenylphosphine, 1.7 ml (12.3 mmols) of triethylamine and 0.76 ml (7.9 mmols) of carbon tetrachloride were added to a solution of 1.84 g (7.9 mmols) of 1-(2-piperidinophenyl)-1-butylamine in 19 ml of acetonitrile, and the mixture was stirred for two days at room temperature. It was then evaporated in vacuo, and the residue was taken up in a mixture of ethyl acetate and water. The organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was purified by chromatography on silica gel (toluene/acetone = 5/1).

Yield: 3 g (81% of theory).

M.p. 113-115°C (petroleum ether).

Calculated: C-72.07%; H-8.21%; N-6.00%.

Found: C-72.18%; H-8.27%; N-6.16%.

The following compounds were prepared by a procedure analogous to that described in Example 1:

(a) Methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 78% of theory.

5 M.p. 82-85°C.

Calculated: C-70.22%; H-7.37%; N-6.82%.

Found: C-70.54%; H-7.49%; N-6.75%.

(b) Ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

10 Prepared from  $\alpha$ -phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 77% of theory.

M.p. 149-151°C.

Calculated: C-74.37%; H-7.25%; N-5.60%.

15 Found: C-74.69%; H-7.44%; N-5.59%.

(c) Methyl 2-methoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from  $\alpha$ -phenyl-2-piperidino-benzylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

20 Yield: 65% of theory.

M.p. 189-190°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.51%; H-6.75%; N-5.86%.

(d) Ethyl 2-ethoxy-4-[N-1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate

25 Prepared from 1-(2-piperidino-phenyl)-1-ethylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 69% of theory.

M.p. 92-93°C.

5      Calculated: C-71.21%; H-7.81%; N-6.39%.

Found: C-71.29%; H-8.03%; N-6.58%.

(e) Ethyl 2-ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate

10      Prepared from 1-(5-chloro-2-piperidino-phenyl)-1-propylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Yield: 80% of theory.

M.p. 110-112°C.

Calculated: C-66.58%; H-7.24%; N-5.75%; Cl-7.28%.

Found: C-66.61%; H-7.34%; N-5.86%; Cl-7.35%.

15      (f) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-pentylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 63% of theory.

20      M.p. 113-115°C.

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.66%; H-8.26%; N-5.99%.

(g) Ethyl 2-ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

25      Prepared from 1-(2-pyrrolidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 50% of theory.

M.p. 85-87°C.

5      Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.90%; H-8.37%; N-6.34%.

(h) Ethyl 2-ethoxy-4-[N-{1-(2-(4-methyl-piperidino)-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

10      Prepared from 1-[2-(4-methyl-piperidino)-phenyl]-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Yield: 44% of theory.

M.p. 127-128°C.

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.20%; H-8.23%; N-5.69%.

15      (i) Ethyl 2-ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-hexamethyleneimino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Yield: 44% of theory.

20      M.p. 97-100°C.

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.41%; H-8.50%; N-5.66%.

(k) Ethyl 2-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

25      Prepared from 1-(4-methyl-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Yield: 68% of theory.

M.p. 113-114°C.

5       Calculated: C-72.47%; H-8.39%; N-5.83%.

Found:       C-72.36%; H-8.31%; N-5.91%.

(1) Ethyl 2-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

10       Prepared from 1-(6-methyl-2-piperidino-phenyl)-1-butyl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 62% of theory.

M.p. <20°C.

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found:       C-72.30%; H-8.50%; N-5.72%.

15       (m) Ethyl 2-ethoxy-4-[N-{1-(6-chloro-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-chloro-2-piperidino-phenyl)-1-butyl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 85% of theory.

20       M.p. <20°C.

Calculated: C-67.12%; H-7.44%; N-5.50%; Cl-7.08%.

Found:       C-67.60%; H-7.77%; N-5.92%; Cl-7.24%.

(n) Ethyl 2-ethoxy-4-[N-{1-(4-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

25       Prepared from 1-(4-methoxy-2-piperidino-phenyl)-1-butyl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 65% of theory.

M.p. 109-110°C.



5        Calculated:    Mol. peak m/e = 496

Found:            Mol. peak m/e = 496

(o)    Ethyl 2-ethoxy-4-[N-{1-(5-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

10        Prepared from 1-(5-methoxy-2-piperidino-phenyl)-1-butyl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield:    31% of theory.

M.p. 117-120°C.

Calculated:    Mol. peak m/e = 496

Found:            Mol. peak m/e = 496

15        (p)    Ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 4-ethoxycarbonyl-3-hydroxy-phenylacetic acid.

Yield:    46% of theory.

20        M.p. 133-134°C.

Calculated:    C-71.21%;    H-7.81%;    N-6.39%.

Found:            C-71.08%;    H-7.91%;    N-6.45%.

(q)    Methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

25        Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield:    67% of theory.

M.p. 128-131°C.

Calculated:    C-71.21%;    H-7.81%;    N-6.39%.

30        Found:            C-71.46%;    H-7.80%;    N-6.07%.

- 5 (r) n-Propyl 2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-n-propoxy-4-n-propoxycarbonyl-phenylacetic acid.

Yield: 56% of theory.

10 M.p. 88-89°C.

Calculated: C-72.84%; H-8.56%; N-5.66%.

Found: C-72.80%; H-8.78%; N-5.78%.

- (s) Ethyl 2-ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

15 Prepared from 5-chloro-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 65% of theory.

M.p. 106-108°C.

Calculated: C-65.41%; H-6.81%; N-6.10%; Cl-7.73%.

20 Found: C-65.81%; H-6.89%; N-6.11%; Cl-7.62%.

- (t) Ethyl (-)-2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from (-)- $\alpha$ -phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

25 Yield: 87% of theory.

M.p. 110-111°C.

Calculated: mol peak m/e = 500

Found: mol peak m/e = 500

Specific rotation:  $[\alpha]_D^{20} = -6.3^\circ$  (c = 1, methanol).

- 5 (u) Ethyl 2-ethoxy-4-[N-(6-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 6-methyl- $\alpha$ -phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 39% of theory.

10 M.p. <20°C.

Calculated: C-74.68%; H-7.44%; N-5.44%.

Found: C-74.81%; H-7.56%; N-5.32%.

- (v) Ethyl 2-ethoxy-4-[N-{ $\alpha$ -(4-methyl-phenyl)-2-piperidino-benzyl}-aminocarbonylmethyl]-benzoate

15 Prepared from  $\alpha$ -(4-methyl-phenyl)-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 34% of theory.

M.p. 150-152°C.

Calculated: C-74.68%; H-7.44%; N-5.44%.

20 Found: C-74.71%; H-7.51%; N-5.29%.

- (w) Ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from  $\alpha$ -phenyl-2-pyrrolidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

25 Yield: 45% of theory.

M.p. 85-87°C.

Calculated: C-74.05%; H-7.04%; N-5.76%.

Found: C-73.95%; H-7.07%; N-5.70%.

- 5 (x) Methyl 2-methoxy-4-[N-(2-hexamethyleneimino- $\alpha$ -phenyl-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 2-hexamethyleneimino- $\alpha$ -phenyl-benzylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 45% of theory.

10 M.p. 181-183°C.

Calculated: C-74.05%; H-7.04%; N-5.74%.

Found: C-74.09%; H-6.62%; N-5.74%.

- (y) Ethyl 2-ethoxy-4-[N-(2-hexamethyleneimino- $\alpha$ -phenyl-benzyl)-aminocarbonylmethyl]-benzoate

15 Prepared from 2-hexamethyleneimino- $\alpha$ -phenyl-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 41% of theory.

M.p. 140-141°C.

Calculated: C-74.68%; H-7.44%; N-5.44%.

20 Found: C-74.46%; H-7.62%; N-5.45%.

- (z) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-toluene

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-methyl-phenylacetic acid.

25 Yield: 55% of theory.

M.p. 107-108°C.

Calculated: C-76.43%; H-8.88%; N-6.86%.

Found: C-76.38%; H-8.99%; N-6.97%.

5 (aa) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-heptyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-heptylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 79% of theory.

10 M.p. 101-104°C.

Calculated: C-73.19%; H-8.72%; N-5.51%.

Found: C-73.00%; H-8.90%; N-5.28%.

Example 2

15 Ethyl (+)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

0.90 g (3.57 mmol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid and 0.61 g (3.73 mmol) of N,N'-carbonyldiimidazole are refluxed for 5 hours in 9 ml of absolute tetrahydrofuran. Then a solution of 0.85 g (3.67 mmol) of (+)-1-(2-piperidino-phenyl)-1-butylamine (ee = 94.2) in 9 ml of absolute tetrahydrofuran is added and the mixture is refluxed for 3 hours. It is concentrated in vacuo and the evaporation residue is distributed between chloroform and water. The organic phase is dried, filtered and evaporated in vacuo. The evaporated extract is purified by column chromatography on silica gel (toluene/acetone = 10.1).

25 Yield: 0.85 g (51.2% of theory).

M.p. 118-119°C (petroleum ether/toluene = 50/2).

5 Calculated: C-72.07%; H-8.21%; N-6.00%.

Found: C-72.43%; H-8.34%; N-6.00%.

Specific rotation:  $[\alpha]_D^{20} = + 7.1^\circ$  (c = 1.06 in methanol).

The following compounds were obtained analogously to  
Example 2:

10 (a) Methyl 3-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and  
2-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 89% of theory.

15 M.p. 102-105°C.

Calculated: C-71.20%; H-7.81%; N-6.39%.

Found: C-71.20%; H-8.02%; N-6.27%.

(b) Ethyl 3-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

20 Prepared from 1-(2-piperidino-phenyl)-1-butylamine and  
2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 73% of theory.

M.p. 136-138°C.

Calculated: C-72.07%; H-8.21%; N-6.00%.

25 Found: C-72.50%; H-8.33%; N-5.95%.

(c) Ethyl 3-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(4-methyl-2-piperidino-phenyl)-1-butyl-  
amine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

5 Yield: 61% of theory.

M.p. 108-110°C.

Calculated: C-72.46%; H-8.39%; N-5.83%.

Found: C-72.50%; H-8.46%; N-5.92%.

10 (d) Ethyl 3-ethoxy-4-[N-(1-(6-methyl-2-piperidino-phenyl)-1-butyl]-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-methyl-2-piperidino-phenyl)-1-butyl-amine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 90% of theory.

M.p. < 20°C.

15 Calculated: C-72.46%; H-8.39%; N-5.83%.

Found: C-72.86%; H-8.20%; N-5.50%.

(e) Methyl 3-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 2-methoxy-4-methoxycarbonyl-phenylacetic acid.

20 Yield: 86% of theory.

M.p. 144-148°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.70%; H-6.85%; N-5.84%.

25 (f) Ethyl 3-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 77% of theory.

30 M.p. 112-115°C.

5      Calculated:    C-74.37%;    H-7.25%;    N-5.60%.

Found:            C-74.69%;    H-7.29%;    N-5.75%.

Example 3

Ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocar-  
bonylmethyl]-benzoate

10            A solution of 4.7 g (20 mmol) of ethyl 2-ethoxy-4-cyano-  
methyl-benzoate and 5.3 g (20 mmol) of  $\alpha$ -phenyl-2-piperidino-  
benzyl alcohol in 30 ml of o-dichlorobenzene was added dropwise  
at 23-25°C to a mixture of 30 ml of concentrated sulfuric acid  
and 30 ml of o-dichlorobenzene. The mixture was stirred for  
15    2 hours at room temperature. Then, the o-dichlorobenzene phase  
was separated, and the residue was added to ice. After the  
aqueous mixture had been made alkaline with a soda solution,  
it was extracted with chloroform. The extracts were dried  
over magnesium sulfate and concentrated by evaporation. The  
20    residue was triturated with petroleum ether (30-60°), filtered  
off and purified on silica gel (toluene/ethylacetate = 5:1) by  
column chromatography.

Yield:    5.6 g (56% of theory).

M.p. 150-151°C.

25      Calculated:    C-74.37%;    H-7.25%;    N-5.60%.

Found:            C-74.59%;    H-7.41%;    N-5.45%.

The following compounds were obtained by a procedure  
analogous to that described in Example 3:



5 (a) Methyl 2-methoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from  $\alpha$ -phenyl-2-piperidino-benzyl alcohol and methyl 4-cyanomethyl-2-methoxy-benzoate.

Yield: 34% of theory.

10 M.p. 189-191°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.63%; H-7.05%; N-5.95%.

(b) 2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

15 Prepared from  $\alpha$ -phenyl-2-piperidino-benzyl alcohol and 2-ethoxy-4-cyanomethyl-benzoic acid.

Extraction at pH 5.

Yield: 47% of theory.

M.p. 154-155°C.

20 Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.61%; H-6.72%; N-5.65%.

(c) 2-Methoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

25 Prepared from  $\alpha$ -phenyl-2-piperidino-benzyl alcohol and 4-cyanomethyl-2-methoxy-benzoic acid.

Extraction at pH 5.

Yield: 30% of theory.

M.p. 202-204°C.

Calculated: C-73.34%; H-6.59%; N-6.11%.

30 Found: C-73.17%; H-6.41%; N-6.05%.

5 (d) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butanol and ethyl-2-ethoxy-4-cyanomethyl benzoate.

Yield: 5% of theory.

10 M.p. 112-114°C.

Calculated: C-72.07%; H-8.21%; N-6.00%.

Found: C-72.29%; H-8.46%; N-6.31%.

(e) Methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoate

15 Prepared from 1-(2-piperidino-phenyl)-1-ethanol and methyl 4-cyanomethyl-2-methoxy-benzoate.

Yield: 18% of theory.

M.p. 83-85°C.

Calculated: C-70.22%; H-7.37%; N-6.82%.

20 Found: C-70.60%; H-7.29%; N-6.97%.

(f) 2-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid

Prepared from 1-(2-piperidino-phenyl)-1-ethanol and 4-cyanomethyl-2-methoxy-benzoic acid.

25 Extraction at pH 5.5.

Yield: 21% of theory.

M.p. 118-120°C.

Calculated: m/e = 396

Found: m/e = 396.

5 (g) Ethyl 2-ethoxy-4-[N-(4-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoate

Prepared from 4-methyl- $\alpha$ -phenyl-2-piperidino-benzyl alcohol and ethyl 2-ethoxy-4-cyanomethyl-benzoate.

Yield: 45% of theory.

10 M.p. 124-125°C.

Calculated: C-74.68%; H-7.44%; N-5.44%.

Found: C-74.81%; H-7.56%; N-5.32%.

(h) Methyl 2-methoxy-4-[N-( $\alpha$ -(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

15 Prepared from  $\alpha$ -(4-chlorophenyl)-2-piperidino-benzyl alcohol and methyl 2-methoxy-4-cyanomethyl-benzoate.

Yield: 47% of theory.

M.p. 176-178°C.

Calculated: C-68.70%; H-6.17%; N-5.53%; Cl-6.99%.

20 Found: C-69.05%; H-5.93%; N-5.76%; Cl-7.10%.

(i) Ethyl 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from  $\alpha$ -phenyl-2-piperidino-benzyl alcohol and ethyl 4-cyanomethyl-2-hydroxy-benzoate.

25 Yield: 78% of theory.

M.p. 172-174°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.80%; H-6.81%; N-5.83%.

5 (k) n-Propyl 2-n-propoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from  $\alpha$ -phenyl-2-piperidino-benzyl alcohol and n-propyl 4-cyanomethyl-2-n-propoxy benzoate.

Yield: 52% of theory.

10 M.p. 119-120°C.

Calculated: C-74.97%; H-7.63%; N-5.30%.

Found: C-74.91%; H-7.72%; N-5.25%.

Example 4

15 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

A mixture of 2 g (4.3 mmols) of ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate and 5.3 ml of 1N sodium hydroxide solution in 20 ml of ethanol was stirred for 3 hours at 60°C, then neutralized with 5.3 ml of 1N hydrochloric acid, and the ethanol was evaporated in vacuo. The residue was taken up in a mixture of ethyl acetate and water, and the organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was crystallized from petroleum ether with the addition of ethanol.

25 Yield: 1.3 g (69% of theory).

M.p. 88-90°C.

Calculated: C-71.21%; H-7.81%; N-6.39%.

Found: C-71.62%; H-7.73%; N-6.54%.

30 The following compounds were obtained by a procedure analogous to that described in Example 4:

- 5 (a) 2-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid x 0.67 H<sub>2</sub>O

Prepared from methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoate.

Yield: 60% of theory.

10 M.p. 116-120°C.

Calculated: C-67.62%; H-7.07%; N-6.85%.

Found: C-67.60%; H-6.87%; N-6.55%.

- (b) 2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory.

M.p. 155-156°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

20 Found: C-73.60%; H-6.96%; N-6.12%.

- (c) 2-Methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

25 Yield: 68% of theory.

M.p. 202-204°C.

Calculated: C-73.34%; H-6.59%; N-6.11%.

Found: C-73.60%; H-6.77%; N-6.20%.

- 5 (d) 2-Ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate.  
Yield: 74% of theory.

10 M.p. 115-118°C.

Calculated: C-65.42%; H-6.81%; N-6.10%; Cl-7.72%.

Found: C-65.54%; H-6.94%; N-5.81%; Cl-7.89%.

- (e) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate.

Yield: 73% of theory.

M.p. 81-83°C.

Calculated: C-70.73%; H-7.60%; N-6.60%.

20 Found: C-70.90%; H-7.47%; N-6.77%.

- (f) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoate.

25 Yield: 92% of theory.

M.p. 82-85°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.45%; H-8.01%; N-6.13%.

- 5 (g) 2-Ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 77% of theory.

10 M.p. 120-123°C.

Calculated: C-70.73%; H-7.60%; N-6.60%.

Found: C-70.71%; H-7.44%; N-6.33%.

- (h) 2-Ethoxy-4-[N-{1-(2-(4-methyl-piperidino)-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-ethoxy-4-[N-{1-(2-(4-methyl-piperidino)-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 71% of theory.

M.p. 83-85°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

20 Found: C-71.60%; H-7.94%; N-6.09%.

- (i) 2-Ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

25 Yield: 81% of theory.

M.p. 101-105°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.31%; H-7.79%; N-6.18%.

- (k) 2-Ethoxy-4-[N-{1-(6-chloro-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

30

Prepared from ethyl 2-ethoxy-4-[N-{1-(6-chloro-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

5 Yield: 82% of theory.

M.p. 133-136°C.

Calculated: C-66.02%; H-7.03%; N-5.92%; Cl-7.50%.

Found: C-66.48%; H-7.47%; N-5.98%; Cl-7.88%.

10 (1) 2-Ethoxy-4-[N-{1-(4-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(4-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory.

M.p. 98-100°C.

15 Calculated: C-69.21%; H-7.74%; N-5.98%.

Found: C-69.12%; H-7.62%; N-5.78%.

(m) 2-Ethoxy-4-[N-{1-(5-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

20 Prepared from ethyl 2-ethoxy-4-[N-{1-(5-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 74% of theory.

M.p. 145-148°C.

Calculated: C-69.21%; H-7.74%; N-5.98%.

Found: C-69.00%; H-7.65%; N-5.89%.

25 (n) 2-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 86% of theory.

30 M.p. 140-143°C.

Calculated: C-70.73%; H-7.60%; N-6.60%.

Found: C-70.49%; H-7.58%; N-6.31%.



- 5 (o) 2-n-Propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from n-propyl 2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory.

10 M.p. 128-132°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.40%; H-7.90%; N-6.47%.

- (p) 2-Ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid x 0.5 H<sub>2</sub>O

15 Prepared from ethyl 2-ethoxy-4-[N-5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 93% of theory.

M.p. 153-155°C.

Calculated: C-62.79%; H-6.41%; N-6.36%; Cl-8.06%.

20 Found: C-63.21%; H-6.34%; N-5.89%; Cl-8.46%.

- (q) 2-Ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

25 Yield: 77% of theory.

M.p. 108-109°C.

Calculated: C-69.68%; H-7.12%; N-7.07%.

Found: C-70.00%; H-7.99%; N-7.31%.

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5 (r) 2-Hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 61% of theory.

10 M.p. 136-138°C.

Calculated: C-70.22%; H-7.37%; N-6.82%.

Found: C-70.40%; H-7.64%; N-6.60%.

(s) 2-Isopropoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-isopropoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 67% of theory.

M.p. 115-118°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

20 Found: C-71.94%; H-7.96%; N-6.04%.

(t) 2-Allyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-allyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

25 Yield: 92% of theory.

M.p. 110-112°C.

Calculated: C-71.97%; H-7.61%; N-6.22%.

Found: C-71.90%; H-7.62%; N-6.21%.

(u) 2-Benzoyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-benzyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 95% of theory.

M.p. 161-163°C.

Calculated: C-74.37%; N-7.25%; N-5.60%.

Found: C-74.40%; N-7.44%; N-5.64%.

(v) (+)-2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl (+)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]benzoate.

Yield: 81% of theory.

M.p. 122-123°C.

Calculated: C-71.21%; H-7.81%; N-6.39%.

Found: C-71.19%; H-7.77%; N-6.29%.

Specific rotation  $[\alpha]_D^{20} = 4.75^\circ$  (c = 1.03 in methanol).

(w) 3-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 3-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 64% of theory.

M.p. 188-191°C.

Calculated: C-70.73%; H-7.60%; N-6.60%.

Found: C-70.88%; H-7.56%; N-6.59%.

- 5 (x) 3-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 3-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 79% of theory.

10 M.p. 159-165°C.

Calculated: C-71.21%; H-7.81%; N-6.39%.

Found: C-71.32%; H-7.62%; N-6.24%.

- (y) 3-Ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 3-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 71% of theory.

M.p. 186-188°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

20 Found: C-71.70%; H-7.86%; N-6.26%.

- (z) 3-Ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 3-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

25 Yield: 65% of theory.

M.p. 174-176°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-72.00%; H-8.10%; N-5.91%.

5 (aa) 2-Ethoxy-4-[N-(4-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(4-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 41% of theory.

10 M.p. 127-129°C.

Calculated: C-74.05%; H-7.04%; N-5.76%.

Found: C-73.80%; H-7.09%; N-5.74%.

(ab) 2-Ethoxy-4-[N(6-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-ethoxy-4-[N-(6-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 40% of theory.

M.p. 118-121°C.

Calculated: C-74.05%; H-7.04%; N-5.76%.

20 Found: C-73.71%; H-6.92%; N-5.76%.

(ac) 2-Ethoxy-4-[N-{ $\alpha$ -(4-methyl-phenyl)-2-piperidino-benzyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{ $\alpha$ -(4-methyl-phenyl)-2-piperidino-benzyl}-aminocarbonylmethyl]-benzoate.

25 Yield: 94% of theory.

M.p. 148-151°C.

Calculated: C-74.05%; H-7.04%; N-5.76%.

Found: C-74.20%; H-7.15%; N-5.81%.

5 (ad) 2-Methoxy-4-[N-( $\alpha$ -(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-( $\alpha$ -(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 77% of theory.

10 m.p. 177-180°C.

Calculated: C-68.21%; H-5.93%; N-5.68%; Cl-7.19%.

Found: C-68.10%; H-5.78%; N-5.53%; Cl-7.43%.

(ae) 2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 67% of theory.

M.p. 141-143°C.

Calculated: C-73.34%; H-6.59%; N-6.11%.

20 Found: C-73.33%; H-6.74%; N-6.02%.

(af) 2-Methoxy-4-[N-(2-hexamethyleneimino- $\alpha$ -phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(2-hexamethyleneimino- $\alpha$ -phenyl-benzyl)-aminocarbonylmethyl]-benzoate.

25 Yield: 90% of theory.

M.p. 154-156°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.70%; H-7.00%; N-5.95%.

5 (ag) 2-Ethoxy-4-[N-(2-hexamethyleneimino- $\alpha$ -phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(2-hexamethyleneimino- $\alpha$ -phenyl-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 75% of theory.

10 M.p. 139-141°C.

Calculated: C-74.05%; H-7.04%; N-5.76%.

Found: C-73.90%; H-7.14%; N-5.79%.

(ah) 2-Hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate by hydrolysis with 4 equivalents of 1N sodium hydroxide in ethanol/dioxane.

Yield: 35% of theory.

M.p. 222-224°C.

20 Calculated: C-72.95%; H-6.35%; N-6.30%.

Found: C-73.00%; H-6.64%; N-6.28%.

(ai) 2-n-Propoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

25 Prepared from n-propyl 2-n-propoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 41% of theory.

M.p. 168-170°C.

Calculated: C-74.05%; H-7.04%; N-5.76%.

Found: C-74.20%; H-7.19%; N-5.57%.

5 (ak) 2-Allyloxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-allyloxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 69% of theory.

10 M.p. 172-173°C.

Calculated: C-74.35%; H-6.66%; N-5.78%.

Found: C-74.11%; H-6.50%; N-5.74%.

(al) 2-Benzyloxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 2-benzyloxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 72% of theory.

M.p. 214-215°C.

Calculated: C-76.38%; H-6.41%; N-5.24%.

20 Found: C-76.18%; H-6.39%; N-5.36%.

(am) (-)-2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl (-)-2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

25 Yield: 89% of theory.

M.p. 90-95°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.59%; H-6.81%; N-5.83%.

Specific rotation:  $[\alpha]_D^{20} = -2.2^\circ$  (c = 1 in methanol).



5 (an) 3-Methoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

Prepared from methyl 3-methoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 72% of theory.

10 M.p. 220-221°C.

Calculated: C-73.34%; H-6.59%; N-6.11%.

Found: C-73.36%; H-6.46%; N-5.85%.

(ao) 3-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

15 Prepared from ethyl 3-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 70% of theory.

M.p. 199-201°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

20 Found: C-73.50%; H-6.74%; N-5.94%.

(ap) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-heptyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-heptyl}-aminocarbonylmethyl]-benzoate.

25 Yield: 88% of theory.

M.p. 71-73°C.

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.28%; H-8.56%; N-5.82%.

5

Example 5

Sodium salt of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid x 1.5 H<sub>2</sub>O

10

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoate analogous to Example 4. After purification by column chromatography the evaporation residue was dissolved in ethanol and mixed with 1 equivalent of 1N sodium hydroxide. By evaporation in vacuo and trituration with acetone, the crystalline sodium salt was obtained.

15

Yield: 76% of theory.

M.p. 242-244°C.

Calculated: C-62.73%; H-7.01%; N-6.01%.

Found: C-62.74%; H-7.17%; N-6.05%.

20

The following compounds were obtained by a procedure analogous to that described in Example 5:

(a) Sodium salt of 2-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid x 0.5 H<sub>2</sub>O

25

Prepared from ethyl 2-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 72% of theory.

M.p. 255-260°C.

Calculated: C-67.06%; H-7.50%; N-5.79%.

Found: C-66.94%; H-7.28%; N-5.50%.

5 (b) Sodium salt of 2-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid  
x 2.5 H<sub>2</sub>O

Prepared from ethyl 2-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

10 Yield: 81% of theory.

M.p. 232-240°C.

Calculated: C-62.39%; H-7.75%; N-5.39%.

Found: C-62.22%; H-7.46%; N-5.61%.

15 (c) Sodium salt of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 87% of theory.

M.p. 250-258°C.

20 Calculated: C-67.79%; H-7.22%; N-6.08%.

Found: C-67.60%; H-7.37%; N-6.04%.

(d) Sodium salt of 2-ethoxy-4-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

25 Prepared from ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory.

M.p. 233-235°C.

Calculated: C-70.42% H-6.32%; N-5.67%.

Found: C-70.20%; H-6.41%; N-5.49%.

5 Example 6

10 Ethyl 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoate

15 1 ml (10.4 mmols) of boron tribromide was added dropwise at -20°C under anhydrous conditions to a stirred solution of 2 g (4 mmols) of ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 20 ml of 1,2-dichloroethane. The mixture was allowed to reach room temperature and was then stirred for 17 hours. It was then poured into ethanol, evaporated in vacuo, ice was added, and the resulting mixture was taken up in a mixture of chloroform and water. The organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 0.37 g (21% of theory).

20 M.p. 172-173°C.

Calculated: C-73.70%; H-6.83%; N-5.93%.

Found: C-73.95%; H-7.05%; N-6.12%.

The following compounds were obtained by a procedure analogous to that described in Example 6:

25 (a) 2-Hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

Prepared from 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid.

Yield: 40% of theory.

30 M.p. 221-223°C.

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6/3/86

Rm

Su

E.G.

Am

5      Calculated:    C-72.95%;    H-6.35%;    N-6.30%.  
Found:            C-72.68%;    H-6.45%;    N-6.49%.

(b) Ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield:    19% of theory.

M.P.    132-134°C

Calculated:    C-71.21;    H-7.81;    N-6.39;

Found:            C-71.43;    H-7.91;    N-6.55;

15      c) 2-Hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Prepared from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Yield:    42 % of theory,

M.p.    136-137°C

Calculated:    C-70.22%;    H-7.37%;    N-6.82%.

Found:            C-70.19%;    H-7.39%;    N-6.99%.

Example 7

25      Tert.butyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

A mixture of 1.9 g (9.6 mmols) of N,N'-dicyclohexyl-carbodiimide, 1.06 ml (11.2 mmols) of absolute tert.butanol and 0.020 g (0.20 mmol) of copper(I) chloride was stirred for 60 hours at room temperature. Then, 6.6 ml of methylene chloride were added, and the resulting solution was added dropwise to a solution of 0.44 g (1 mmol) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid in 15 ml of methylene chloride. After 60 hours' stirring at 20°C, the precipitate which had formed was filtered off, washed with methylene chloride, and the methylene chloride solution was evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (chloroform/ethyl acetate =9/1).

5 Yield: 0.30 g (60% of theory).

M.p. 74-77°C (from petroleum ether).

Calculated: C-72.84%; H-8.56%; N-5.66%.

Found: C-73.00%; H-8.65%; N-5.79%.

Example 8

10 Ethyl 2-benzyloxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-  
carbonylmethyl]-benzoate

0.10 g (2.3 mmols) of sodium hydride (55% in oil) was added to a solution of 1.1 g (2.3 mmols) of ethyl 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 10 ml of anhydrous dimethylformamide and the resulting mixture was stirred for half an hour at room temperature. Then, a solution of 0.27 ml (2.3 mmols) of benzyl bromide in 5 ml of anhydrous dimethylformamide was added dropwise, and the resulting mixture was stirred for 5 hours at room temperature. It was then evaporated in vacuo, the residue was taken up in a mixture of dilute sodium hydroxide and chloroform, and the organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was recrystallized from acetonitrile.

20 Yield: 0.9 g (69.5% of theory).

25 M.p. 156-157°C.

Calculated: C-76.84%; H-6.81%; N-4.98%.

Found: C-76.94%; H-6.95%; N-4.87%.

The following compounds were obtained by a procedure analogous to that described in Example 8:

- 5 (a) Ethyl 2-allyloxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate, using allyl bromide.

Yield: 46% of theory.

10 M.p. 117-119°C.

Calculated: C-74.97%; H-7.08%; N-5.47%.

Found: C-74.90%; H-7.14%; N-5.38%.

- (b) Ethyl 2-isopropoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

15 Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate, using 1.5 equivalents of isopropyl bromide at 150°C.

Yield: 56% of theory.

M.p. 98-99°C.

20 Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.60%; H-8.60%; N-5.75%.

- (c) Ethyl 2-allyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

25 Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate, using allyl bromide.

Yield: 72% of theory.

M.p. 105-106°C.

Calculated: C-72.77%; H-8.00%; N-5.85%.

30 Found: C-72.90%; H-7.90%; N-5.87%.

5 (d) Ethyl 2-benzyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate, using benzyl bromide.

10 Yield: 80% of theory.

M.p. 135-136°C.

Calculated: C-74.97%; H-7.63%; N-5.30%.

Found: C-75.20%; H-7.78%; N-5.59%.

Example 9

15 n-Propyl 2-n-propoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 2-hydroxy-4-(N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl)-benzoic acid analogous to Example 8, using 2 equivalents of sodium hydride and 2 equivalents of n-propyl bromide.

20 Yield: 45% of theory.

M.p. 118-120°C.

Calculated: C-74.97%; H-7.63%; N-5.30%.

Found: C-75.20%; H-7.80%; N-5.41%.

25 The following compound was obtained by a procedure analogous to that described in Example 9:

(a) n-Propyl 2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

30 Prepared from n-propyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.



5 Yield: 39% of theory.

M.p. 89-90°C.

Calculated: C-72.84%; H-8.56%; N-5.66%.

Found: C-72.95%; H-8.77%; N-5.59%.

Example 10

10 Ethyl 2-ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

15 1.0 g (2.18 mmols) of ethyl 2-ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate was hydrogenated in 20 ml of ethanol with 0.5 g of 10% palladium-on-charcoal at 50°C under 1 bar of hydrogen for 45 minutes. The reaction mixture was filtered through diatomaceous earths, the filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (chloroform/methanol - 10/1).

20 Yield: 0.71 g (77% of theory).

M.p. 83-84°C (from petroleum ether).

Calculated: C-70.73%; H-7.60%; N-6.60%.

Found: C-70.89%; H-7.66%; N-6.76%.

25 The following compound was obtained by a procedure analogous to that described in Example 10:

(a) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate.

5 Yield: 74% of theory.

M.p. 115-117°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.47%; H-8.11%; N-6.25%.

Example 11

10 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-amino-carbonylmethyl]-benzoic acid (form A)

(a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoic acid.

15 Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoate.

Yield: 85% of theory.

M.p. 110-113°C.

Calculated: C-71.97%; H-7.61%; N-6.22%.

Found: C-71.92%; H-7.80%; N-5.98%.

20 (b) 0.21 g (0.39 mmol) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoic acid were hydrogenated in 10 ml of absolute ethanol with 0.10 g of 10% palladium-on-charcoal at 50°C and a pressure of 1 bar of hydrogen for 7 hours. The reaction mixture was then filtered

25 through diatomaceous earth, the reaction filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (chloroform/methanol = 10/1).

Yield: 0.10 g (47% of theory).

M.p. 90-92°C (recrystallized from acetone/petroleum ether).

5 Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.50%; H-8.12%; N-6.45%.

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, is also obtained in other solid forms when it is crystallized from other solvents or mixtures of solvents. Form (B), which has a melting point of 140 to 142°C, is obtained by crystallization from an ethanol/water mixture. The foamy form (C), which has a melting point range from 75 to 85°C, is obtained from the 1:1 methanol adduct (melting point: 85 to 90°C), which occurs upon crystallization from methanol, by heating at 60°C in vacuo (5 Torr) over phosphorus pentoxide, whereby the methanol is removed.

In the dissolved state these forms are identical, as is evident from the corresponding solution spectra, for instance the IR-spectra in methylene chloride shown in Figs. 1, 2 and 3 of the attached drawings. However, in the solid state, the three forms differ in their melting characteristics and their solid spectra, for instance as shown by the corresponding IR-KBr-spectra in Figs. 4, 5 and 6 of the attached drawings.

In order to measure infra-red absorption, forms (A), (B) and (C) were dissolved in methylene chloride (40 mg of substance per ml of methylene chloride), or intimately triturated with potassium bromide and then compressed hydraulically to form a tablet (approx. 1 mg of substance/300 mg of KBr).

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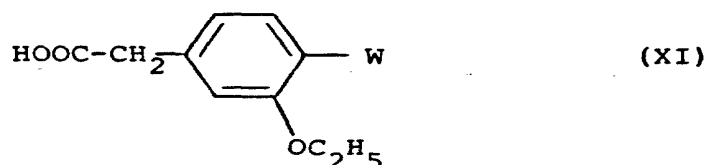
5           In the case of the solutions, the IR-spectra were  
measured with an IR-spectrometer (Perkin Elmer Tyoe 299) in  
a cell of sodium chloride (layer thickness 0.2 mm) by compari-  
son with a pure methylene chloride solution and, in the case  
of the potassium bromide tablets, with an IR-spectrometer  
10 (Perkin Elmer Type 298) by comparison with air.

The three solid forms can be converted into one another  
by suitable recrystallization and drying. Thus, the low-  
melting-point form (A) is obtained by recrystallizing the  
high-melting-point form (B) from acetone/petroleum ether and  
15 the high-melting-point form (B) is obtained by recrystallizing  
the low-melting-point form (A) from ethanol/water. By recrys-  
tallizing the high-melting-point form (B) from methanol, a  
1:1 adduct with methanol is obtained, and from this the foamy  
form (C) is obtained by removing the methanol.

20           Irrespective of the particular process which is used to  
synthesize 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-  
butyl}-aminocarbonylmethyl]-benzoic acid, therefore, the  
high-melting-point or low-melting-point or foamy form can be  
obtained, as desired, by a suitable choice of solvent or  
25 mixture of solvents during crystallization and by suitable  
drying. This is important in the practical use of the solid  
forms, whether or not they are accompanied by galenic excipients  
in pharmaceutical compositions, particularly for lowering  
blood sugar in the treatment of Type II diabetes; this is

5 because different solid forms may have different shelf lives and/or different absorption characteristics in vivo and may thus give a different pattern of biological activity.

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid may be obtained by the  
10 methods described hereinabove, but preferably by reacting 3-methyl-1-(2-piperidino-phenyl)-1-butylamine with a compound of the formula



wherein W is carboxyl or carboxyl protected by a protective group or with a reactive derivative thereof, optionally  
20 prepared in the reaction mixture, followed, if necessary, by removal of the protective group, and the solid forms (B) and (C) are obtained by suitable subsequent crystallization, suitable final recrystallization and/or drying.

25 Examples of reactive derivatives of a compound of the formula XI include the esters such as the methyl, ethyl and benzyl esters thereof, the thioesters such as the methylthio and ethylthioesters, the halides such as the acid chloride, the anhydrides and imidazolides thereof.

The reaction is advantageously carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride,

5 ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile  
or dimethylformamide, optionally in the presence of an acid-  
activating agent or a dehydrating agent, for instance in the  
presence of ethyl chloroformate, thionyl chloride, phosphorus  
10 trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodi-  
imide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide,  
N,N'-carbonyldiimidazole, N,N'-thionyl-diimidazole or triphenyl-  
phosphine/carbon tetrachloride, or in the presence of an  
amino group activating agent, such as phosphorus trichloride,  
and optionally in the presence of an inorganic base such as  
15 sodium carbonate or a tertiary organic base such as triethyl-  
amine or pyridine, which may simultaneously serve as solvent,  
at temperatures between -25 and 250°C, but preferably at  
temperatures between -10°C and the boiling point of the solvent  
which is used. The reaction may also be carried out without  
20 a solvent, and any water formed during the reaction may be  
removed by azeotropic distillation, for instance by heating  
with toluene, using a water trap, or by adding a drying agent  
such as magnesium sulfate or a molecular sieve.

25 The subsequent removal of the protective group is  
preferably carried out by hydrolysis, either in the presence  
of an acid such as hydrochloric, sulfuric, phosphoric or  
trichloroacetic acid, or in the presence of a base such as  
sodium hydroxide or potassium hydroxide, in a suitable solvent  
such as water, methanol, methanol/water, ethanol, ethanol/

5 water, water/isopropanol or water/dioxane at temperatures between -10 and 120°C, for instance at temperatures between room temperature and the boiling point of the reaction mixture.

10 A tert.butyl protective group may also be removed thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane, and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulfonic, sulfuric, phosphoric or polyphosphoric acid.

15 Moreover, a benzyl protective group may also be removed by hydrogenation in the presence of a hydrogenation catalyst such as palladium-on-charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide.

20 The subsequent crystallization is carried out in situ from the reaction mixture containing ethanol/water or, as a final recrystallization, by dissolving the reaction product in a mixture of ethanol and water, optionally while heating, and cooling, optionally accompanied by trituration and/or seeding (form B), or by dissolving the reaction product in 25 acetone and adding petroleum ether (form A), or by dissolving the reaction product, optionally while heating in methanol, subsequent cooling of the solution accompanied by trituration and/or seeding, and heating the isolated solid methanol adducts, preferably in vacuo, in the presence of a drying agent such as

5 phosphorus pentoxide (form C).

10 Like the other compounds of the formula I, solid forms (A), (B) and (C) of 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid may also be converted into their salts, particularly their non-toxic, pharmacologically acceptable table salts with inorganic or organic acids or bases. Suitable acids for this purpose are, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, tritaric, succinic, maleic or fumaric acid, and suitable bases are sodium hydroxide, potassium hydroxide, calcium hydroxide, cyclohexylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine or lysine.

15 The melting points in Examples 12-16 were determined in an Electrothermal<sup>®</sup> melting point apparatus with visual observation of the sample of product in a capillary tube fused at one end.

20 Example 12

Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoate

25 3 g (11.9 mmols) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 3.7 g (14.3 mmols) of triphenylphosphine, 3.3 ml (23.8 mmols) of triethylamine and 1.15 ml (11.9 mmols) of carbon tetrachloride were added successively to a solution of 2.9 g (11.9 mmols) of 3-methyl-1-(2-piperidino-phenyl)-1-butylamine in 29 ml of acetonitrile. The mixture was then stirred for



5 15 hours at room temperature, the solvent was removed in vacuo,  
and the residue was taken up in a mixture of ethyl acetate  
and water. The organic phase was dried over sodium sulfate,  
filtered and concentrated by evaporation in vacuo. The  
10 evaporation residue was purified by column chromatography on  
silica gel (toluene/acetone = 10/1).

Yield: 4.9 g (85% of theory).

M.p. 143-145°C (petroleum ether).

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.37%; H-8.45%; N-6.07%.

15 Example 13

High-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-  
phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

A mixture of 4.7 g (9.7 mmols) of ethyl 2-ethoxy-4-[N-  
{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-  
20 benzoate and 14.7 ml of 1N sodium hydroxide was stirred in 47  
ml of ethanol for 2 hours at 60°C, then neutralized with 14.7  
ml of 1N hydrochloric acid and cooled to 0°C. The mixture was  
filtered to remove the precipitated colorless crystals, and the  
crystals were washed with ice water and with a little ice cold  
25 ethanol and then dried at 100°C/1 Torr.

Yield: 3.9 g (88% of theory).

M.p. 140-142°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.90%; H-8.08%; N-6.34%.

5           Upon further recrystallization from ethanol/water (2/1)  
the melting point remained constant.

Example 14

Low-melting-point form (A) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

10           1.0 g of the high-melting-point form (B) of 2-ethoxy-4-  
[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonyl-  
methyl]-benzoic acid was dissolved at room temperature in 5 ml  
of acetone, and 5 ml of petroleum ether (m.p. 60-70°C) were  
added. Upon trituration, crystallization gradually set in.  
15           The same quantity of petroleum ether was added again, and after  
crystallization had ended, the mixture was filtered. The  
crystals were washed with petroleum ether, and the almost  
colorless crystals were dried for 2 hours at 60°C/0.1 Torr.  
Yield: 0.7 g.

20           M.p. 95-98°C (clear beginning at 135°C).

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found:           C-71.80%; H-8.04%; N-5.92%.

          The IR-spectra for this form (see Figs. 1 and 4) are  
identical to the IR-spectra for the form (A), melting point  
25           90-92°C, described in Example 11(b) above.

Example 15

High-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

          1.0 g of the low-melting-point form (A) of 2-ethoxy-4-

5 [N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-amino-  
carbonylmethyl]-benzoic acid was dissolved in 10 ml of  
ethanol/water (2/1) while heating over a steam bath. The  
solution was then cooled to 0°C, whereupon crystallization  
began. The mixture was filtered, and the residue was washed  
10 with a little ice-cold ethanol and dried at 100°C/1 Torr.  
Yield: 0.8 g.  
M.p. 140-142°C.

Example 16

Foamy form (C) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-  
15 3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

1.5 g of the high-melting-point form (B) of 2-ethoxy-  
4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonyl-  
methyl]-benzoic acid was dissolved in 5 ml of methanol while  
heating. The solution was then cooled to 0°C with trituration.  
20 The crystals precipitated thereby were separated by filtration,  
washed with a little cold methanol, and dried for 2 hours at  
60°C/0.1 Torr.

Yield of adduct (with 1 x CH<sub>3</sub>OH): 1.2 g.

M.p. 85-90°C.

25 Calculated: (x 1 CH<sub>3</sub>OH): C-69.39%; H-8.32%; N-5.78%.

Found: C-69.20%; H-8.20%; N-5.92%.

The adduct was converted into the methanol-free foamy  
form (C) by heating for 24 hours at 60°C/5 Torr over phosphorus  
pentoxide.

5 Melting range: 75-85°C.

Calculated: C-71.65%; H-8.02%; N-6.19%.

Found: C-71.82%; H-8.06%; N-6.03%.

Example 17

10 Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoate, melting point 125-126°C, which in turn was prepared from (2-piperidino-phenyl)-isobutyl-ketimine and 3-ethoxy-4-ethoxy-carbonyl-phenyl-acetic acid analogous to Example 1.

15 Yield: 51% of theory.

M.p. 139-141°C.

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.30%; H-8.20%; N-5.87%.

20 Example 18

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzyl alcohol

25 A solution of 1.8 g (3.6 mmols) of ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 20 ml of absolute tetrahydrofuran was added dropwise at -5°C to a mixture of 0.28 g (7.4 mmols) of lithium aluminum hydride and 50 ml of absolute tetrahydrofuran, and the resulting mixture was stirred for 3 hours at 0°C. It was then diluted with absolute ether, and 4N sodium hydroxide was added. The

5 mixture was filtered through diatomaceous earth, the filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).

Yield: 0.51 g (31% of theory).

10 M.p. 133-135°C.

Calculated: C-75.95%; H-7.47%; N-6.11%.

Found: C-75.97%; H-7.55%; N-5.95%.

The following compound was obtained by a procedure analogous to that described in Example 18:

15 (a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzyl alcohol

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate by reduction with lithium borohydride in boiling tetrahydrofuran in the presence of 10% of trimethyl borate.

20 Yield: 68% of theory.

M.p. 112-115°C.

Calculated: C-73.55%; H-8.55%; N-6.60%.

Found: C-73.60%; H-8.38%; N-6.69%.

25 Example 19

2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzaldehyde

A solution of 0.4 g (0.87 mmol) of 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzyl

5 alcohol was added dropwise at room temperature to a stirred  
solution of 0.28 g (1.3 mmols) of pyridinium chlorochromate  
in 5 ml of chloroform. The reaction mixture was stirred  
overnight at room temperature, evaporated in vacuo, the  
10 residue was mixed with ether, the ethereal mixture was filtered,  
the filtrate was evaporated in vacuo, and the residue was  
purified by column chromatography on silica gel (toluene/  
ethyl acetate = 2/1).

Yield: 0.16 g (40% of theory).

M.p. 154-156°C.

15 Calculated: C-76.29%; H-7.06%; N-6.14%.

Found: C-76.30%; H-7.15%; N-6.10%.

The following compound was obtained by a procedure  
analogous to that described in Example 19:

20 (a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-  
carbonylmethyl]-benzaldehyde

Prepared from 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-  
butyl}-aminocarbonylmethyl]-benzyl alcohol.

Yield: 47% of theory.

M.p. 109-111°C.

25 Calculated: C-73.90%; H-8.11%; N-6.63%.

Found: C-74.22%; H-8.14%; N-6.73%.

Example 20

2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonyl-  
methyl]-benzaldehyde

0.67 g (5.6 mmols) of sodium carbonate was heated together with 6 ml of ethylene glycol on an oil bath at 170°C, and then, while rapidly stirring, 0.70 g (1.1 mmols) of N<sup>1</sup>-[2-ethoxy-4-{N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl}-benzoyl]-N<sup>2</sup>-tosyl-hydrazine were added thereto within a minute; a violent evolution of gas was observed. Then, the mixture was heated for 2 minutes more at 170°C and then poured immediately over ice. The aqueous mixture was extracted with ether, and the extract was dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).

Yield: 0.25 g (50% of theory).

M.p. 153-156°C.

Calculated: C-76.29%; H-7.06%; N-6.14%.

Found: C-76.42%; H-7.33%; N-6.28%.

The following compound was obtained by a procedure analogous to that described in Example 20:

(a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzaldehyde

Prepared from N<sup>1</sup>-[2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoyl]-N<sup>2</sup>-tosyl-hydrazine.

Yield: 51% of theory.

M.p. 108-111°C.

Calculated: C-73.90%; H-8.11%; N-6.63%.

Found: C-73.79%; H-8.29%; N-6.75%.

5

Example 21

Benzyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzoate

0.35 g (0.8 mmol) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid was refluxed together with 0.15 g (0.9 mmol) of N,N'-carbonyldiimidazole in 15 ml of absolute tetrahydrofuran for 2 hours. Then, 1.03 ml (10 mmols) of benzyl alcohol were added, and the mixture was refluxed for 3.5 hours. The reaction mixture was then evaporated in vacuo, and the residue was purified by column chromatography on silica gel (chloroform/acetone = 9/1). Yield: 0.10 g (23.6% of theory).

M.p. < 20°C.

Calculated: Mol peak m/e = 528.

Found: Mol peak m/e = 528.

20

Example 22

Ethyl (+)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

and

Ethyl (-)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

25

28 mg of ethyl (±)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate were added in 0.02 mg- portions to a chiral phase HPLC column made by the Baker Co., in which (R)-N-3,5-dinitrobenzoyl-phenylglycine was covalently



5 bonded to aminopropyl-silica gel (5  $\mu$ m particle size, spherical,  
pore size 60Å; 4.6 mm internal diameter, 25 cm in length).  
Flow agent: hexane/ethanol = 100/5.  
Flow rate: 0.75 ml/minute.  
Temperature: 22°C.

10 The fractions eluted at 31.2 minutes and at 32.9 minutes  
(UV detection at 254 nm) were separately recovered, collected  
and evaporated in vacuo.

The following was obtained from the 31.2-minute eluate:  
7.5 mg of ethyl (+)-2-ethoxy-4-[N-{1-(2-piperidino-  
15 phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.  
M.p. 117-119°C.

Specific rotation:  $[\alpha]_D^{20} = + 7.0^\circ$  (c = 1.03 in methanol).

The following was obtained from the 32.9-minute eluate:  
9.4 mg of ethyl (-)-2-ethoxy-4-[N-{1-(2-piperidino-  
20 phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.  
m.p. 115-117°C.

Specific rotation:  $[\alpha]_D^{20} = - 6.9^\circ$  (c = 1.02 in methanol).

Analogous to Example 22,

25 (a) Ethyl ( $\pm$ )-2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-  
aminocarbonylmethyl]-benzoate

was separated into its (+) enantiomer and its (-) enantiomer.

Example 23

Ethyl 2-acetoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-  
carbonylmethyl]-benzoate

5           A mixture of 0.20 g (0.46 mmol) of ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate, 0.34 ml (3.65 mmols) of acetic acid anhydride and 20 µl of concentrated sulfuric acid was stirred for 40 hours at 70°C. The mixture was then evaporated in vacuo, the residue was taken up in a mixture of water and ether, and neutralized with sodium carbonate. The ethereal phase was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 10/1).  
10  
15           Yield: 50% of theory.

M.p. 133-135°C (from petroleum ether).

Calculated: C-69.98%; H-7.55%; N-5.83%.

Found: C-69.75%; H-7.32%; N-5.74%.

20           The following compounds were obtained by a procedure analogous to that described in Example 23:

(a) 2-Acetoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzoic acid

25           Prepared from 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid.

Yield: 12% of theory.

M.p. 125-127°C.

Calculated: Mol peak m/e = 452.

Found: Mol peak m/e = 452.

5 (b) Ethyl 2-acetoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 23.5% of theory.

10 M.p. 163-166°C.

Calculated: C-72.35%; H-6.66%; N-5.44%.

Found: C-72.41%; H-6.75%; N-5.31%.

(c) 2-Acetoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

15 Prepared from 2-hydroxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid.

Yield: 17% of theory.

M.p. 126-128°C.

Calculated: C-71.58%; H-6.21%; N-5.76%.

20 Found: C-71.77%; H-6.57%; N-5.81%.

Example 24

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-toluene

25 A mixture of 0.54 g (1.2 mmols) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzyl chloride (melting point 114-115°C, prepared from 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzyl alcohol and thionyl chloride in chloroform) and 10 ml of absolute dioxane was hydrogenated for 3 hours at 20°C and a

5 pressure of 5 bar hydrogen. The reaction mixture was then  
evaporated in vacuo, and the residue was taken up in a mixture  
of ethyl acetate and aqueous sodium carbonate. The organic  
phase was dried, filtered and evaporated in vacuo. The evapor-  
10 ation residue was purified by column chromatography on silica  
gel (chloroform/acetone = 19/1).

Yield: 0.23 g (47% of theory).

M.p. 107-108°C.

Calculated C-76.43%; H-8.88%; N-6.86%.

Found: C-76.40%; H-8.88%; N-6.90%.

15 Example 25

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl-  
methyl]-benzoic acid

100 mg (0.20 mmol) of tert.butyl 2-ethoxy-4-[N-{1-(2-  
piperidino-phenyl)-1-butyl}-aminocarbonyl]-benzoate were  
20 refluxed in 5 ml of benzene together with a few crystals of  
p-toluene-sulfonic acid hydrate for half a day. The desired  
product was obtained, as confirmed by thin-layer chromatography,  
by the  $R_f$ -value and mass spectrum.

M.p. 87-89°C.

25 Calculated: m/e = 438.

Found: m/e = 438.

Example 26

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl-  
methyl]-benzoic acid

5           0.25 g (0.47 mmol) of benzyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate was hydrogenated in 10 ml of ethanol with 0.12 g of 10% palladium-on-charcoal at 50°C and a pressure of 5 bar of hydrogen. After 5 hours the catalyst was filtered off  
10 through diatomaceous earth, and the filtrate was evaporated in vacuo. The evaporation residue was crystallized from petroleum ether/ethanol.

Yield: 0.14 g (70% of theory).

M.p. 87-90°C.

15           Calculated: C-71.21%; H-7.81%; N-6.39%.

Found: C-71.46%; H-7.95%; N-6.51%.

Example 27

Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-n-hexyl}-aminocarbonylmethyl]-benzoate

20           Prepared from 1-(2-piperidino-phenyl)-1-n-hexylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid analogous to Example 1.

Yield: 43% of theory.

M.p. 101-105°C

25           Calculated: C-72.84%; H-8.56%; N-5.66%.

Found: C-72.72%; H-8.52%; N-5.63%.

Example 28

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-n-hexyl}-aminocarbonylmethyl]-benzoic acid

0094503.100797  
/62001.2054630

5

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-n-hexyl}-aminocarbonylmethyl]-benzoate analogous to Example 4.

Yield: 77% of theory.

M.p. 117-120°C.

10

Calculated: C-72.07%; H-8.21%; N-6.00%.

Found: C-72.00%; H-8.06%; N-5.90%.

Example 29

[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-phenyl]-acetonitrile

To a solution of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl chloride (2 g; 4.5 mmol) [prepared from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl alcohol with thionyl chloride in chloroform], is added sodium cyanide (0.255 g, 5.2 mmol), dissolved in water (2.2 ml), and the phase transfer catalyst benzyl tributylammonium chloride (0.069 g, 0.22 mmol) and the mixture is stirred for 5 days at ambient temperature. Then, further phase transfer catalyst (0.069 g) is added, together with a few small grains of potassium iodide and sodium cyanide (0.2 g) in water (1 ml) and the mixture is stirred for a further 24 hours; then the same amounts of these three components are added again and the mixture is stirred for a further 12 hours. Methylene chloride (40 ml) is added and the mixture is extracted twice with water. The methylene chloride phase is dried over sodium sulphate/potassium carbonate, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 1.53 g,

Melting point: 116-118°C (methylene chloride/ether).

Calculated: C 74.79 H 8.14 N 9.69

Found: 74.86 8.19 9.42

Example 30

[2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetonitrile

A solution of 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzyl chloride (2.6 g, 5.45 mmol) in dimethylsulphoxide (10 ml) is added dropwise at 50-60°C to sodium cyanide (0.32 g, 6.5 mmol) in dimethylsulphoxide (40 ml). The mixture is then stirred for 5 hours at 60°C, added to water and extracted with chloroform. The extract is concentrated by evaporation *in vacuo*. The residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 1.2 g,

Melting point: 145-148°C

Calculated: C 77.05 H 7.11 N 8.99

Found: 76.92 7.05 8.78

Example 31

Ethyl [2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-acetate

Dry hydrogen chloride is introduced for 3 hours into a stirred and boiling solution of [2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-acetonitrile (1.3 g, 3 mmol) in absolute ethanol (30 ml). The mixture is then evaporated down *in vacuo*, water (25 ml) is added to the evaporation residue and this is stirred for 15 minutes at 50°C. The mixture is adjusted to a pH of 7 by the addition of solid sodium hydrogen carbonate and is extracted three times with ethyl acetate. The combined organic extracts are shaken once with water, then dried over sodium sulphate/potassium carbonate, filtered and



concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 9/1).

Yield: 1.0 g,

Melting point: 91-93°C (petroleum ether)

Calculated: C 72.47 H 8.39 N 5.83

Found: 72.73 8.68 5.71

#### Example 32

##### Methyl

[2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-phenyl]-acetate

Dry hydrogen chloride is introduced for 4 hours into a stirred and refluxed solution of [2-ethoxy-4-(N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetonitrile (1.2 g, 2.57 mmol) in methanol (20 ml). The mixture is then concentrated by evaporation, added to water and extracted with chloroform. The extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 4/1).

Yield: 340 mg,

Melting point: 136-138°C (acetonitrile/water)

Calculated: molecular peak m/e = 500

Found: molecular peak m/e = 500

#### Example 33

[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl-amino-carbonylmethyl)-phenyl]-acetic acid

A 1N sodium hydroxide solution (2.8 ml) is added to ethyl [2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-

butyl-aminocarbonylmethyl]-phenyl]-acetate (0.67 g, 1.4 mmol) in ethanol (10 ml) and stirred for 4 hours at ambient temperature. Then the mixture is evaporated down in vacuo at 50°C. Water and a few drops of methanol are added to the evaporation residue which is then adjusted to pH 6 with 1N acetic acid. It is cooled in ice, whereupon a precipitate is formed. This is filtered off and recrystallised from ethanol.

Yield: 0.47 g,

Melting point: 158-159°C (ethanol)

Calculated: C 71.65 H 8.02 N 6.19

Found: 71.35 8.30 6.21

#### Example 34

##### [2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetic acid

Prepared analogously to Example 5 by alkaline saponification of methyl [2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetate.

Melting point: 146-148°C

Calculated: C 74.05 H 7.04 N 5.76

Found: 73.70 7.00 5.85

#### Example 35

##### Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate

A solution of ethyl diethyl-phosphono-acetate (1.68 g, 7.5 mmol) in absolute dioxan (3 ml) is slowly added dropwise, with vigorous stirring, to a suspension of 55% sodium hydride (in oil) (0.327 g, 7.5 mmol) in absolute dioxan (4 ml). After the reaction has died down the mixture is heated

to 80°C for a further 45 minutes. It is then cooled to ambient temperature, a solution of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzaldehyde (2.11 g, 5 mmol) [prepared from the corresponding benzyl alcohol by oxidation with pyridinium chlorochromate in chloroform] in absolute dioxan (4 ml) is added dropwise thereto and the mixture is heated for 2 hours at 50°C. The reaction mixture is poured onto ice/water and extracted with chloroform. The organic extract is dried and filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 19/1).

Yield: 1.64 g,

Melting point: 130-131°C (ether)

Calculated: C 73.14 H 8.18 N 5.69

Found: 73.36 8.34 5.75

#### Example 36

#### 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid nitrile

Prepared analogously to Example 7 from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzaldehyde with diethylphosphonoacetonitrile.

Melting point: 125-128°C (petroleum ether)

Calculated: C 75.47 H 7.92 N 9.43

Found: 75.40 7.95 9.24

#### Example 37

#### Ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamate

Under a nitrogen atmosphere, 50% sodium hydride

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(0.19g, 8 mmol) is added to a stirred solution of ethyl diethylphosphono-acetate (1.8 g, 8 mmol) in absolute 1,2-dimethoxy-ethane (10 ml). Then a solution of 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzaldehyde (2 g, 4.4 mmol) in absolute 1,2-dimethoxy-ethane (15 ml) is added and the mixture is stirred for 30 minutes at ambient temperature. It is concentrated by evaporation in vacuo and the evaporation residue is distributed between water and chloroform. The chloroform extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 0.37 g,

Melting point: 111-113°C (cyclohexane)

Calculated: C 75.26 H 7.27 N 5.32

Found: 75.14 7.32 5.25

#### Example 38

##### 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-cinnamic acid

A solution of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl-methyl]-cinnamate (0.49 g, 1 mmol) in ethanol (10 ml) is stirred together with 1N sodium hydroxide solution (2 ml) for 3 days at ambient temperature. The mixture is then concentrated by evaporation in vacuo, water and a few drops of methanol are added to the evaporation residue and this is then adjusted to pH 6 with 1N acetic acid. The precipitate is filtered off, dried and recrystallised from ethyl acetate.

Yield: 0.37 g,

Melting point: 175-177°C (decomp.)

Calculated: C 72.39 H 7.81 N 6.03

Found: 72.50 7.88 6.06

Example 39

2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid

Ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamate (330 mg, 0.62 mmol) is dissolved in ethanol (10 ml) and, after the addition of 4N sodium hydroxide solution (4 ml), stirred for 3 hours at 50°C. Then the mixture is neutralized with 4N hydrochloric acid (4 ml), diluted with water and filtered off from the precipitate. It is then recrystallized from aqueous ethanol.

Yield: 210 mg,

Melting point: 181°C

Calculated: C 74.67 H 6.87 N 5.62

Found: 74.72 6.76 5.42

Example 40

Ethyl 3-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionate

A solution of of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate (0.54 g, 1.1 mmol) in ethanol (15 ml) is hydrogenated for 1 hour at ambient temperature and under 3 bars of hydrogen on 10% palladium/charcoal (0.1 g). The mixture is filtered, concentrated by evaporation in vacuo and the evaporation residue is crystallized from petroleum ether.

Yield: 0.30 g,

Melting point: 71-73°C

Calculated: C 72.84 H 8.56 N 5.66

Found: 73.19 8.54 5.70

Example 41

Ethyl 3-[2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionate

Prepared analogously to Example 12 by catalytic hydrogenation of ethyl 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamate and subsequent purification by column chromatography on silica gel (cyclohexane/ethyl acetate/methanol = 6/1/0.5).

Melting point: 130°C (ethanol/water)

Calculated: C 74.97 H 7.63 N 5.30

Found: 74.65 7.61 5.15

Example 42

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared analogously to Example 12 by catalytic hydrogenation of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid.

Melting point: 112-114°C

Calculated: C 72.07 H 8.21 N 6.00

Found: 72.30 8.42 6.19

Example 43

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionitrile

Prepared analogously to Example 12 by catalytic hydrogenation of 2-ethoxy-4-[N-(1-(2-piperidino-

phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid nitrile.

Melting point: 102-103°C (petroleum ether)

Calculated: molecular peak m/e = 447

Found: molecular peak m/e = 447

#### Example 44

##### 3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared analogously to Example 5 by alkaline saponification of ethyl 3-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionate and subsequent purification by column chromatography (chloroform/methanol = 9/1).

Melting point: 112-115°C (petroleum ether)

Calculated: C 72.07 H 8.21 N 6.00

Found: 72.40 8.21 6.03

#### Example 45

##### 3-[2-Ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared analogously to Example 5 by alkaline saponification of ethyl 3-[2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-propionate.

Melting point: 74°C

Calculated: C 74.37 H 7.25 N 5.60

Found: 74.29 7.31 5.27

#### Example 46

##### 3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionitrile

At ambient temperature, p-toluenesulphonic acid chloride (45.8 mg, 0.24 mmol) is added to a mixture

of 3-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid amide, (56 mg, 0.12 mmol) melting point 153-155°C [prepared from the corresponding propionic acid by reacting with carbonyldiimidazole and then with ammonia in tetrahydrofuran] and absolute pyridine (0.044 ml). The mixture is stirred for 45 minutes at 20°C and for 2 hours at 50 to 60°C. After cooling, water is added, the mixture is made alkaline with concentrated ammonia and extracted three times with chloroform. The combined chloroform extracts are washed with water, dried over sodium sulphate, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 9/1).

Yield: 11 mg,

Calculated: molecular peak m/e = 447

Found: molecular peak m/e = 447

#### Example 47

#### Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a solution of  $\alpha$ -cyclohexylmethyl-2-piperidino-benzylamine (1.13 g, 3.96 mmol) in acetonitrile (11 ml) are added, successively, 3-ethoxy-4-ethoxycarbonyl-phenyl acetic acid (1 g, 3.96 mmol), of triphenylphosphine (1.25 g, 4.76 mmol), triethylamine (1.11 ml, 7.92 mmol) and carbon tetrachloride (0.38 ml, 3.96 mmol) and the mixture is stirred for 15 hours at ambient temperature. It is then concentrated by evaporation in vacuo and partitioned between ethyl acetate and water. The organic extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 10/1).



Yield: 1.4 g,  
Melting point: 95-97°C (petroleum  
ether/cyclohexane =1/1)  
Calculated: C 73.81 H 8.52 N 5.38  
Found: 73.98 8.49 5.61

Example 48

Ethyl 2-ethoxy-4-[N-( $\alpha$ -benzyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from  $\alpha$ -benzyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Melting point: 102-105°C (petroleum ether)  
Calculated: C 74.68 H 7.44 N 5.44  
Found: 74.73 7.68 5.39

Example 49

2-Ethoxy-4-[N-( $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclohexyl-methyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (1.15 g, 2.21 mmol) in ethanol (12 ml) are stirred together with 1N sodium hydroxide solution (3.3 ml) for 2 hours at 50°C. Then 1N hydrochloric acid (3.3 ml) is added and the mixture is cooled in ice. The precipitate formed is filtered off, washed with a little ice cold ethanol and dried in vacuo at 100°C.  
Yield: 0.9 g,  
Melting point: 153-156°C  
Calculated: C 73.14 H 8.18 N 5.69  
Found: 73.30 8.17 5.66

Example 50

2-Ethoxy-4-[N-( $\alpha$ -benzyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-( $\alpha$ -benzyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.  
Melting point: 100-105°C

Calculated: C 74.05 H 7.04 N 5.76  
Found: 73.77 7.10 5.50

Example 51

Ethyl 2-ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a mixture of (2-piperidino-phenyl)-glycine-ethyl ester-dihydrochloride (2 g, 5.96 mmol) in acetonitrile (12 ml) are added successively 3-ethoxy-4-ethoxycarbonyl-phenyl-acetic acid, (1.52g, 5.96 mmol) triphenylphosphine (1.77 g, 6.75 mmol), triethylamine (2.45 ml, 17.9 mmol) and carbon tetrachloride (0.57 ml, 5.96 mmol) and the mixture is stirred overnight at ambient temperature. It is then concentrated by evaporation in vacuo and partitioned between chloroform and water. The organic extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 4/1).  
Yield: 1.2 g,

Melting point: 100-103°C (ether)  
Calculated: C 67.72 H 7.31 N 5.64  
Found: 67.87 7.46 5.61

Example 52

Benzyl 2-ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-  
benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 23 from (2-piperidino-phenyl)-glycine-ethyl ester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenyl acetic acid.

Melting point: 90-93°C

Calculated: molecular peak m/e = 558

Found: molecular peak m/e = 558

Example 53

Benzyl

2-ethoxy-4-[N-( $\alpha$ -methoxycarbonyl-2-piperidino-  
benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 23 from (2-piperidino-phenyl)-glycine-methyl ester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenyl acetic acid.

Melting point: 100-102°C (ether)

Calculated: C 70.57 H 6.66 N 5.14

Found: 70.46 6.67 5.14

Example 54

Benzyl

2-ethoxy-4-[N-( $\alpha$ -propoxycarbonyl-2-piperidino-  
benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 23 from (2-piperidino-phenyl)-glycine-n-propylester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenylacetic acid.

Melting point: 100-102°C (petroleum ether)

Calculated: C 71.31 H 7.04 N 4.89

Found: 71.62 7.01 4.97

Example 55

Benzyl 2-ethoxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 23 from (2-piperidino-phenyl)-glycine-isopropylester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenylacetic acid.  
Melting point: 85-88°C (acetone/petroleum ether)  
Calculated: C 71.31 H 7.04 N 4.89  
Found: 71.64 7.10 4.77

Example 56

Ethyl 4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoate

Prepared analogously to Example 23 from (2-piperidino-phenyl)-glycine-ethylester-dihydrochloride and 4-ethoxycarbonyl-3-hydroxy-phenylacetic acid.  
Melting point: 107-110°C (petroleum ether)  
Calculated: C 66.65 H 6.88 N 5.98  
Found: 66.60 6.86 6.03

Example 57

Ethyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

First, 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid (2.52 g, 10 mmol) and N,N'-carbonyldiimidazole (1.62 g, 10 mmol) are heated to 70°C for 45 minutes in absolute tetrahydrofuran (15 ml). A solution of 2-hydroxy-1-(2-piperidino-phenyl)-1-ethylamine (2.07 g, 9.4 mmol) [prepared by reducing (2-piperidino-phenyl)-glycine-ethylester with lithium aluminium hydride in ether] in absolute tetrahydrofuran (7 ml) is added thereto and the mixture is refluxed for 1 hour. After standing

overnight it is diluted with ethyl acetate (50 ml) and shaken twice with water (30 ml). The organic phase is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/methanol = 19/1).

Yield: 2.4 g.

Melting point: 127-128°C (acetone)

Calculated: C 68.70 H 7.54 N 6.16

Found: 68.80 7.58 6.15

#### Example 58

##### Benzyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 29 from 3-ethoxy-4-benzyloxycarbonyl-phenylacetic acid and 2-hydroxy-1-(2-piperidino-phenyl)-1-ethylamine.

Melting point: 89-91°C (acetone/ether)

Calculated: C 72.07 H 7.02 N 5.42

Found: 72.10 7.15 5.29

#### Example 59

##### 2-Ethoxy-4-[N-( $\alpha$ -carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Ethyl 2-ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.45 g, 0.9 mmol) in ethanol (5 ml) is stirred together with 1N sodium hydroxide solution (2.7 ml) for 2 hours at 50°C. Then 1N hydrochloric acid (2.7 ml) is added and the mixture is concentrated by evaporation in vacuo. The evaporation residue is partitioned between water and chloroform. The combined chloroform extracts are shaken once with water, then the organic phase is dried, filtered and evaporated

down in vacuo. The evaporation residue is crystallized with ether.

Yield: 0.27 g,

Melting point: 222-225°C (decomp.)

Calculated: C 65.44 H 6.41 N 6.36

Found: 65.58 6.59 6.28

Example 60

4-[N-( $\alpha$ -Carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoic acid

Prepared analogously to Example 31 by alkaline saponification of ethyl 4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxybenzoate.

Melting point: 220-228°C

Calculated: C 64.07 H 5.87 N 6.79

Found: 63.84 5.95 7.13

Example 61

2-Ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 31 by alkaline saponification of ethyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate and purification by column chromatography on silica gel (chloroform/ethanol = 95/5).

Melting point: 80-81°C (decomp., sintering from 75°C)

Calculated: molecular peak m/e = 426

Found: molecular peak m/e = 426

Example 62

Ethyl 2-ethoxy-4-[N-( $\alpha$ -carboxy-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoate

Ethyl 2-ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-

benzyl)-aminocarbonylmethyl]-benzoate (0.45 g, 0.9 mmol) in ethanol (5 ml) is stirred together with 1N sodium hydroxide solution (0.90 ml) for 4 hours at ambient temperature. Then 1N hydrochloric acid (0.90 ml) is added and the mixture is evaporated down in vacuo. The residue is partitioned between water and chloroform, the chloroform solution is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethanol = 5/1).

Yield: 0.23 g,

Melting point: 177-180°C (ether)

Calculated: C 66.65 H 6.88 N 5.98

Found: 66.65 7.11 5.79

#### Example 63

##### Ethyl 4-[N-( $\alpha$ -carboxy-2-piperidino-benzyl)-aminocarbonyl-methyl]-2-hydroxy-benzoate

Prepared analogously to Example 34 by alkaline saponification of ethyl 4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoate.

Melting point: 156-159°C (ether)

Calculated: C 65.44 H 6.41 N 6.36

Found: 65.66 6.38 6.33

#### Example 64

##### Benzyl 2-ethoxy-4-[N-( $\alpha$ -carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 34 by alkaline saponification of benzyl 2-ethoxy-4-[N-( $\alpha$ -methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in dioxan.

Melting point: 140-142°C

Calculated: C 70.17 H 6.46 N 5.28

Found: 70.21 6.50 5.31

Example 65

Ethyl 2-ethoxy-4-[N-( $\alpha$ -acetoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a solution of of ethyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.227 g, 0.5 mmol) and absolute triethylamine (0.126 ml, 0.9 mmol) in absolute chloroform (3 ml), a solution of acetyl chloride (0.063 ml, 0.9 mmol) in absolute chloroform (1 ml) is added dropwise. After 4 days' stirring at ambient temperature the mixture is diluted with chloroform, washed with dilute aqueous sodium bicarbonate solution, the chloroform solution is dried and filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/acetone = 4/1).

Yield: 0.17 g,

Melting point: 107-109°C (ether/petroleum ether)

Calculated: C 67.72 H 7.31 N 5.64

Found: 67.70 7.48 5.74

Example 66

Benzyl 2-ethoxy-4-[N-( $\alpha$ -acetoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 37 from benzyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate with acetyl chloride.

Calculated: molecular peak m/e = 558

Found: molecular peak m/e = 558



Example 67

Benzyl 2-ethoxy-4-[N-( $\alpha$ -propionyloxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 37 from benzyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate with propionyl chloride.

Melting point: 73-74°C

Calculated: C 71.31 H 7.04 N 4.89

Found: 71.20 7.10 4.61

Example 68

2-Ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

A solution of benzyl 2-ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.140 g, 0.25 mmol) in ethanol (1.4 ml) is hydrogenated with 10% palladium/charcoal (0.03 g) for 4.5 hours at 50°C under 5 bar of hydrogen. The mixture is filtered, evaporated down in vacuo and the evaporation residue is purified by column chromatography on silica gel (chloroform/methanol = 10/1).

Yield: 0.041 g,

Melting point: 115-118°C (petroleum ether)

Calculated: molecular peak m/e = 468

Found: molecular peak m/e = 468

Example 69

2-Ethoxy-4-[N-( $\alpha$ -methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 40 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-( $\alpha$ -methoxycarbonyl-2-piperidino-benzyl)-aminocarbonyl-

methyl]-benzoate in methanol.  
Melting point: 147-150°C (decomp.) (ether)  
Calculated: C 66.06 H 6.65 N 6.16  
Found: 66.28 6.56 5.90

Example 70

2-Ethoxy-4-[N-( $\alpha$ -n-propoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 40 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-( $\alpha$ -n-propoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in n-propanol.  
Melting point: 122-125°C (ether/petroleum ether = 1/1)  
Calculated: C 67.20 H 7.10 N 5.80  
Found: 67.39 7.24 5.78

Example 71

2-Ethoxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 40 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in isopropanol.  
Melting point: 149-151°C (acetone/petroleum ether)  
Calculated: C 67.20 H 7.10 N 5.80  
Found: 67.50 6.99 5.78

Example 72

2-Ethoxy-4-[N-( $\alpha$ -acetoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 40 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-( $\alpha$ -acetoxymethyl-2-piperidino-benzyl)-aminocarbonyl-

methyll]-benzoate in ethanol.

Calculated: molecular peak m/e = 468

Found: molecular peak m/e = 468

Example 73

2-Ethoxy-4-[N-( $\alpha$ -propionyloxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 40 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-( $\alpha$ -propionyloxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in ethanol.

Melting point: 64-67°C (ethanol/water)

Calculated: molecular peak m/e = 482

Found: molecular peak m/e = 482

Example 74

2-Hydroxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Boron tribromide (0.04 ml, 0.414 mmol) is added at -20°C with the exclusion of moisture to a stirred solution of 2-ethoxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid (0.20 g, 0.414 mmol) in 1,2-dichloroethane (5 ml). The mixture is allowed to come up to ambient temperature and is then stirred for 2 hours. It is poured into isopropanol, the mixture is concentrated by evaporation in vacuo, water is added and the mixture is extracted with chloroform. The organic extract is dried and filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform methanol/glacial acetic acid = 5/1/0.01).

Yield: 0.14 g,

Melting point: 190-200°C (ether)

Calculated: molecular peak m/e = 454

Found: molecular peak m/e = 454

Example 75

Ethyl 2-ethoxy-4-[N-( $\alpha$ -ethoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Ethyl 2-ethoxy-4-[N-( $\alpha$ -hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.64 g, 1.4 mmol) is added with stirring at ambient temperature to sodium hydride (0.061 g, 1.4 mmol) (55% in oil) in absolute tetrahydrofuran (6.4 ml). The mixture is stirred for 1 hour, then ethyl iodide (0.113 ml, 1.4 mmol) is added and the mixture is stirred for a further 16 hours at ambient temperature. Then ethanol (2 ml) is added and the mixture is evaporated down in vacuo. The evaporation residue is partitioned between chloroform and water. The organic phase is washed twice with water, dried, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/acetone = 17/3).

Yield: 0.05 g,

Melting point: 85-87°C (petroleum ether)

Calculated: molecular peak m/e = 482

Found: molecular peak m/e = 482

Example 76

2-Ethoxy-4-[N-( $\alpha$ -ethoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 31 by alkaline saponification of ethyl 2-ethoxy-4-[N-( $\alpha$ -ethoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Calculated: molecular peak m/e = 454

Found: molecular peak m/e = 454

Example 77

4-[N-( $\alpha$ -Carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoic acid

Prepared analogously to Example 46 by reacting 2-ethoxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid with 2.5 equivalents of boron tribromide in methylene chloride. Melting point: 220-230°C (water)  
Calculated: C 64.07 H 5.87 N 6.79  
Found: 64.21 5.99 6.81

Example 78

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionitrile

Magnesium chips (0.11 g, 4.5 mmol) are added to 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid nitrile (0.05 g, 0.11 mmol) in methanol (1.1 ml) and the mixture is stirred for 45 minutes at 25°C and for 1 hour at 0°C. It is then cooled to 0°C and mixed with of 1N hydrochloric acid (4.5 ml). It is diluted with water, filtered over kieselguhr and extracted with chloroform. The chloroform extract is washed with aqueous sodium bicarbonate solution, dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 9/1).  
Yield: 0.015 g,  
Melting point: 102-104°C (petroleum ether)  
Calculated: molecular peak m/e = 447  
Found: molecular peak m/e = 447

Example 79

[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-phenyl]-acetonitrile

Prepared analogously to Example 1 from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzyl chloride with sodium cyanide.

Melting point: 135-136°C

Calculated: C 75.13 H 8.33 N 9.39

Found: 75.12 8.18 9.18

Example 80

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from  $\alpha$ -cyclopropylmethyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 126-127°C

Calculated: C 72.77 H 8.00 N 5.85

Found: 72.85 7.74 5.84

Example 81

2-Ethoxy-4-[N-( $\alpha$ -cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid hemihydrate

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 103-104°C

Calc. (x 0.5 H<sub>2</sub>O): C 70.55 H 7.68 N 6.10

Found: 70.67 7.67 6.37

Example 82

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclobutylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from  $\alpha$ -cyclobutylmethyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenyl acetic acid.

Melting point: 116-118°C

Calculated: C 73.14 H 8.18 N 5.69

Found: 73.14 8.32 5.64

Example 83

2-Ethoxy-4-[N-( $\alpha$ -cyclobutylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclobutylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 140-142°C

Calculated: C 72.39 H 7.81 N 6.03

Found: 72.15 7.79 5.97

Example 84

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclopentylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from  $\alpha$ -cyclopentylmethyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenyl-acetic acid.

Melting point: 120-121°C

Calculated: C 73.49 H 8.36 N 5.53

Found: 73.31 8.55 5.39

Example 85

2-Ethoxy-4-[N-( $\alpha$ -cyclopentylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethox-4-[N-( $\alpha$ -cyclopentyl-methyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoate.

Melting point: 85-88°C

Calculated: C 72.77 H 8.00 N 5.85

Found: 72.50 8.02 6.03

Example 86

Ethyl 2-ethoxy-4-[N-(2-piperidino- $\alpha$ -(tetrahydrofuran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from 2-piperidino- $\alpha$ -(tetrahydrofuran-2-yl-methyl)-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenyl-acetic acid.

Melting point: 111-113°C

Calculated: C 70.84 H 7.93 N 5.51

Found: 70.76 7.73 5.51

Example 87

2-Ethoxy-4-[N-(2-piperidino- $\alpha$ -(tetrahydrofuran-2-ylmethyl)-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(2-piperidino- $\alpha$ -(tetrahydrofuran-2-yl-methyl)-benzyl)-amino-carbonylmethyl]-benzoate.

Melting point: 121-123°C

Calculated: C 69.98 H 7.55 N 5.83

Found: 69.90 7.78 5.71



Example 88

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cycloheptylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from  $\alpha$ -cycloheptylmethyl-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 96-98°C

Calculated: C 74.12 H 8.67 N 5.24

Found: 74.40 8.87 5.39

Example 89

2-Ethoxy-4-[N-( $\alpha$ -cycloheptylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-( $\alpha$ -cycloheptylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 127-130°C

Calculated: C 73.49 H 8.36 N 5.53

Found: 73.54 8.62 5.47

Example 90

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

a) Ethyl 2-ethoxy-4-[N-( $\alpha$ -(cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from  $\alpha$ -cyclohexylmethyl-(2-piperidino-phenyl)-ketimine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 85-88°C

Calculated: C 74.10 H 8.16 N 5.10

Found: 74.37 8.00 5.45

According to the 80 MHz-<sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>) there is a mixture of E/Z = 1/2. [Olefinic H: (E) D 6.26, (Z) 5.42 ppm].

b) Ethyl 2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 12 by catalytic hydrogenation of ethyl 2-ethoxy-4-[N-(α-(cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Melting point: 95-97°C

Calculated: C 73.81 H 8.52 N 5.38

Found: 73.92 8.74 5.29

#### Example 91

2-Ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

a) 2-Ethoxy-4-[N-(α-(cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-(cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 95-100°C

Calculated: C 73.44 H 7.81 N 5.71

Found: 73.38 7.73 5.75

b) 2-Ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 12 by catalytic hydrogenation of 2-ethoxy-4-[N-(α-(cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid.

Melting point: 154-156°C  
Calculated: C 73.14 H 8.18 N 5.69  
Found: 73.31 8.25 5.71

Example 92

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from 1-(2-piperidino-phenyl)-3-buten-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Melting point: 110-112°C  
Calculated: C 72.39 H 7.81 N 6.03  
Found: 72.10 7.66 5.94

Example 93

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]-benzoate.  
Melting point: 92-95°C  
Calculated: C 71.53 H 7.39 N 6.42  
Found: 71.27 7.42 6.42

Example 94

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from 3-methyl-1-(2-piperidino-phenyl)-3-buten-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.  
Melting point: 126-128°C  
Calculated: C 72.77 H 8.00 N 5.85

Found: 72.82 8.22 5.78

Example 95

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 64-66°C

Calculated: C 71.97 H 7.61 N 6.22

Found: 71.70 7.50 5.98

Example 96

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-2-buten-1-yl)-aminocarbonylmethyl]-benzoate [with 25% of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate]

Prepared analogously to Example 19 from 3-methyl-1-(2-piperidino-phenyl)-2-buten-1-yl-amine [containing 25% of 3-methyl-1-(2-piperidino-phenyl)-1-butylamine] and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 141-142°C

Calculated: C 72.77 H 8.00 N 5.85

Found: 72.60 7.77 5.73

The mixing ratio of 75/25 is obtained from the corresponding ratio of intensities of the particularly characteristic signals in the 400 MHz-<sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>). The position of the signals is: 3-methyl-2-buten-1-yl compound: olefinic H: 5.25 (d), CH<sub>3</sub>: 1.64 (s) and 1.77 (s), benzylic >CH- 6.00 (t), benzylic CH<sub>2</sub>-: 3.52 ppm (s) 3-methyl-1-butyl compound: CH<sub>3</sub>: 0.90 (d),

benzylic  $>\text{CH}-$  5.35 (m), benzylic  $-\text{CH}_2-$ : 3.54 ppm (s).

Example 97

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-2-buten-1-yl)-aminocarbonylmethyl]-benzoic acid  
[containing 25% of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid]

Prepared analogously to Example 21 by alkaline saponification of the corresponding ethyl ester mixture from Example 68.

Melting point: 154-156°C

Calculated: C 71.97 H 7.61 N 6.22

Found: 71.80 7.57 5.98

Example 98

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyne-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from 1-(2-piperidino-phenyl)-3-butyne-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 86-90°C

Calculated: C 72.70 H 7.41 N 6.06

Found: 72.60 7.40 6.04

Example 99

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyne-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyne-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 66-69°C

Calculated: C 71.87 H 6.96 N 6.45

Found: 71.60 6.95 6.38

Example 100

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from 1-(2-piperidino-phenyl)-4-penten-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 117-120°C

Calculated: C 72.77 H 8.00 N 5.85

Found: 72.73 7.97 6.07

Example 101

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 82-85°C

Calculated: C 71.97 H 7.61 N 6.22

Found: 71.97 7.59 5.98

Example 102

Ethyl 2-ethoxy-4-[N-(1-(2-piperidino- $\alpha$ -(tetrahydropyran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 19 from 2-piperidino- $\alpha$ -(tetrahydropyran-2-yl-methyl)-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 82-85°C

Calculated: C 71.24 H 8.10 N 5.36

Found: 71.28 7.96 5.29

Example 103

2-Ethoxy-4-[N-(1-(2-piperidino- $\alpha$ -(tetrahydropyran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino- $\alpha$ -(tetrahydropyran-2-yl-methyl)-benzyl)-aminocarbonyl-methyl]-benzoate.

Melting point: 140-142°C (sinters from 70°C, partial softening at 105°C)

Calculated: C 70.42 H 7.74 N 5.66

Found: 7.88 5.40

Ethyl 2-ethoxy-4-[N-( $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

At 23-25°C, a solution of ethyl 2-ethoxy-4-cyanomethyl-benzoate (2.35 g, 10 mmol) and  $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl alcohol (2.88 g, 10 mmol) in o-dichlorobenzene (15 ml) is added dropwise to a mixture of concentrated sulphuric acid (15 ml) and o-dichlorobenzene (15 ml). The mixture is stirred for 2 hours at ambient temperature. The o-dichlorobenzene phase is then separated off and the residue is added to ice. After being made alkaline with soda solution, it is extracted with chloroform. The extracts are dried over sodium sulphate and concentrated by evaporation. The residue is purified by column chromatography on silica gel (toluene/acetone = 10/1). Yield: 1.1 g

Melting point: 95-97°C

Calculated: C 73.81 H 8.52 N 5.38

Found: 73.95 8.64 5.42

Example 105

Benzyl 2-ethoxy-4-[N-( $\alpha$ -methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Potassium carbonate (0.28 g, 2 mmol) is added to a solution of benzyl 2-ethoxy-4-[N-( $\alpha$ -carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (1.06 g, 2 mmol) in anhydrous dimethyl formamide (8 ml). The mixture is stirred for 10 minutes at ambient temperature, then methyl iodide (0.125 ml, 2 mmol) is added and the resulting mixture is stirred overnight at ambient temperature. It is filtered and the filtrate is concentrated by evaporation to dryness in vacuo. The evaporation residue is partitioned between aqueous sodium bicarbonate solution (pH = 9) and methylene chloride. The organic phase was poured over sodium sulphate, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 4/1) and crystallised from ether/petroleum ether.

Yield: 0.56 g,

Melting point: 100-102°C

Calculated: C 70.57 H 6.66 N 5.14

Found: 70.69 6.71 5.29

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Example 106

(S) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid

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a) (S)-3-Methyl-1-(2-piperidino-phenyl)-1-butylamine

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Equimolar quantities of racemic 3-methyl-1-(2-piperidino-phenyl)-1-butylamine and of N-acetyl-L-glutamic acid were refluxed in acetone, whereby methanol was added in such an amount to yield a clear solution.

After cooling over night up to 20°C, the obtained crystals were suction filtered and twice washed with acetone cooled to -15°C. The obtained product [M.p.: 163-166°C;  $[\alpha]_D^{20} = +0,286^\circ$  (c = 1 in methanol)] was recrystallised from acetone under addition of methanol, whereby (S)-3-methyl-1-(2-piperidino-phenyl)-1-butylamine as N-acetyl-L-glutamic acid addition salt was obtained in a yield of 60,4 % of theory.

M.p.: 168-171°C

$[\alpha]_{20}^D = +0,356^\circ$  (c = 1 in methanol)

The free amine was obtained after reacting with sodium hydroxide solution.

b) (S) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoate

---

Prepared from (S)-3-Methyl-1-(2-piperidino-phenyl)-1-butyl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid analogously to Example 1.

Yield: 77 % of theory,

M.p.: 121-123°C (petroleum ether/aceton = 7/1)

$[\alpha]_D^{20} = +7,82^\circ$  (c = 1 in methanol)

c) (S) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid

---

Prepared from (S) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoate by saponification analogously to Example 4.

Yield: 75,9 % of theory,

M.p.: 102-104°C (petroleum ether/toluene),

$[\alpha]_{20}^D = +7,80^\circ$  (c = 1,025 in methanol).

15 The compounds of the present invention, that is, those  
embraced by formula I above, including forms (A), (B) and (C)  
of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-  
aminocarbonylmethyl]-benzoic acid, their enantiomers and their  
non-toxic, pharmacologically acceptable salts formed with  
inorganic or organic acids or bases, have useful pharmacody-  
namic properties. More particularly, they have a favorable  
effect on the intermediate metabolism and exhibit hypoglycemic  
20 acitivity in warm-blooded animals such as rats.

25 The hypoglycemic activity of the compounds of the  
instant invention was ascertained by the standard pharmaco-  
logical test method described below, and the table which  
follows shows the results of this test for a few representative  
species of the genus, where

A = 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-  
aminocarbonylmethyl]-benzoic acid,

B = 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-  
aminocarbonylmethyl]-benzoic acid,

- 5 C = 2-methoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
- D = 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
- 10 E = (+)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid,
- F = 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid,
- G = sodium 2-ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate,
- 15 H = 2-ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid,
- I = 2-methoxy-4-(N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl)-benzoic acid,
- K = 2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid,
- 20 L = 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoic acid,
- M = 2-ethoxy-4-[N-(4-methyl- $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
- 25 N = form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid,

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- O = [2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-phenyl]-acetonitrile,
- P = [2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-phenyl]acetonitrile,
- Q = 2-ethoxy-4-[N-( $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
- R = 2-ethoxy-4-[N-( $\alpha$ -ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
- S = 2-ethoxy-4-[N-( $\alpha$ -methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,
- T = 2-ethoxy-4-[N-( $\alpha$ -isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,
- U = 2-ethoxy-4-[N-( $\alpha$ -cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,
- V = 2-ethoxy-4-[N-( $\alpha$ -(tetrahydrofuran-2-yl-methyl)-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,
- W = 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]benzoic acid,
- X = 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]benzoic acid and
- Y = 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyn-1-yl)-aminocarbonylmethyl]benzoic acid,

Test for Hypoglycemic Activity

5 The hypoglycemic activity of the test compounds was ascertained on female rats of a particular strain weighing from 180-220 g which had been fasted for 24 hours before the start of the test. The test compounds were suspended in 1.5% methyl cellulose immediately before the start of the test and administered by esophageal tube.

10 Blood samples were taken immediately before the administration of the test compound and 1, 2, 3 and 4 hours afterwards, in each case from the retroorbital Venous plexus. 50  $\mu$ l of each sample were deproteinated with 0.5 ml of 0.33 N perchloric acid and centrifuged. The glucose in the supernatant fluid was measured using the hexokinase method with the aid of an analytical photometer. The statistical evaluation was made using the t-test according to Student with  $p = 0.05$  as the limit of significance.

15 The following tables show the change in glucose content in percent compared with the control:

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Table I

Compound	1 mg/kg				0.5 mg/kg			
	1	2	3	4 h	1	2	3	4 h
A	-37	-46	-23	-14				
B	-38	-49	-38	-33	-43	-36	-34	-35
C	-38	-41	-38	-34				
D	-42	-54	-37	-34				
E					-40	-39	-36	-36
F	-44	-44	-40	-30				
G					-40	-33	-30	-17
H					-42	-34	-18	n.s.
I					-42	-39	-37	-30
K					-34	-36	-24	n.s.
L					-42	-45	-38	-39
M	-44	-41	-35	-27				
O	-29	-37	-35	-34				
P	-12	-10	-14	-14				
Q						-22	-47	-45 -45
R	-33	-17	n.s.	n.s.				
S	-42	-35	-28	-18				
T	-36	-21	-18	n.s.				
U						-45	-45	-36 -36
V						-46	-25	-13 -10
W						-42	-39	-28 -35
X						-44	-41	-31 -28
Y						-33	-18	-11 n.s.

n.s. = not statistically significant

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25

Table II

Compound	0.1 mg/kg			
	1	2	3	4 h.
N	-38	-44	-41	-40

In the tests for hypoglycemic activity, no toxic side effects were observed, even at a dosage of 10 mg/kg p.o., with any of these compounds.



5           The novel compounds are virtually non-toxic; for example, after a single dose of 2,000 mg/kg p.o. (suspension in 1% methyl cellulose) of compounds B and D to 5 male and 5 female mice, only one animal in this group died during the observation period of 14 days.

10           The toxic effect of a single dose of compound N administered orally (suspended in 1% methyl cellulose) was tested in male and female mice of our own strain weighing from 20-26 g over an observation period of 14 days.

Table III

15

Compound	Approximate acute toxicity
N	>1000 mg/kg p.o. (0 out of 6 animals died)

20           By virtue of their pharmacological properties, the compounds of the present invention are useful for the treatment of diabetes mellitus.

25           For pharmaceutical purposes the compounds of the present invention are administered to warm-blooded animals perorally or parenterally as active ingredients in customary pharmaceutical compositions, that is, compositions consisting essentially of an inert pharmaceutical carrier and an effective amount of the active ingredient, such as tablets, coated pills, capsules, wafers, powders, solutions, suspensions, emulsions, syrups and the like. An effective amount of the compounds of the present

5 invention is from 0.014 to 0.71 mgm/kg body weight, preferably  
0.035 to 0.29 mgm/kg body weight, once or twice daily.

The following examples illustrate a few pharmaceutical  
compositions comprising a compound of the present invention  
as an active ingredient and represent the best modes contem-  
10 plated of using the invention. The parts are parts by weight  
unless otherwise specified.

Example 107

Tablets containing 5 mg of 2-ethoxy-4-[N-(1-(2-piperidino-  
phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid,  
15 form (B)

The tablet composition is compounded from the following  
ingredients:

Active ingredient	(1)	5.0 parts
Corn starch	(2)	62.0 "
20 Lactose	(3)	48.0 "
Polyvinylpyrrolidone	(4)	4.0 "
Magnesium stearate	(5)	<u>1.0 "</u>
		120.0 parts

Preparation:

25 Ingredients (1), (2), (3) and (4) are mixed together and  
moistened with water. The moist mixture is passed through a  
1.5 mm mesh screen and dried at about 45°C. The dry granulate  
is passed through a 1.0 mm mesh screen and mixed with ingre-  
dient (5). The finished mixture is compressed into 120 mg-  
30 tablets.

5

Example 108

Coated tablets containing 2.5 mg of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, form (A)

10

The tablet core composition is compounded from the following ingredients:

15

Active ingredient	(1)	2.5 parts
Potato starch	(2)	44.0 "
Lactose	(3)	30.0 "
Polyvinylpyrrolidone	(4)	3.0 "
Magnesium stearate	(5)	0.5 "
		<hr/> 80.0 parts

Preparation:

20

Ingredients (1), (2), (3) and (4) are thoroughly mixed and moistened with water. The moist mass is passed through a 1 mm-mesh screen, dried at about 45°C, and the granulate is then passed through the same screen. After ingredient (5) has been added, convex 80 mg-tablet cores are compressed in a tablet-making machine. The tablet cores thus produced are covered in known manner with a coating consisting essentially of sugar and talc. The finished tablets are polished with wax. Weight of each coated tablet: 120 mg.

25

Example 109

Tablets containing 10 mg of 2-ethoxy-4-[N-( $\alpha$ -phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

5 The tablet composition is compounded from the following ingredients:

Active ingredient	10.0 parts
Powdered lactose	70.0 "
Corn starch	31.0 "
Polyvinylpyrrolidone	8.0 "
Magnesium stearate	1.0 "
	<hr/>
	120.0 parts

10 Preparation:

15 The mixture of active ingredient, lactose and corn starch is moistened with a 20% solution of polyvinylpyrrolidone in water. The moist mass is passed through a 1.5 mm mesh screen and dried at 45°C. The dried granulate is passed through a 1 mm mesh screen and is homogeneously mixed with magnesium stearate. The composition is compressed into 120 mg-tablets.

20 Example 110

Coated tablets containing 5 mg of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

25 The tablet core composition is compounded from the following ingredients:

Active ingredient	5.0 parts
Secondary calcium phosphate	70.0 "
Corn starch	50.0 "
Polyvinylpyrrolidone	4.0 "
Magnesium stearate	1.0 "
	<hr/>
	130.0 parts

5

Preparation:

10

The mixture of active ingredient, calcium phosphate and corn starch is moistened with a 15% solution of polyvinylpyrrolidone in water. The moist mass is passed through a 1 mm mesh screen, dried at 45°C and then passed through the same screen. After adding the magnesium stearate, 130 mg-tablet cores are compressed from the mixture.

15

A coating of sugar and talc is applied in known manner to the cores thus produced. The finished coated tablets are polished with wax.

Weight of coated tablet: 180 mg.

20

Any one of the other compounds embraced by formula I, including forms (A), (B) and (C) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, an enantiomer thereof or a non-toxic, pharmacologically acceptable salt thereof may be substituted for the particular active ingredient in Examples 29 through 32. Likewise, the amount of active ingredient in these illustrative examples may be varied to achieve the dosage unit range set forth above, and the amounts and nature of the inert pharmaceutical carrier ingredients may be varied to meet particular requirements.

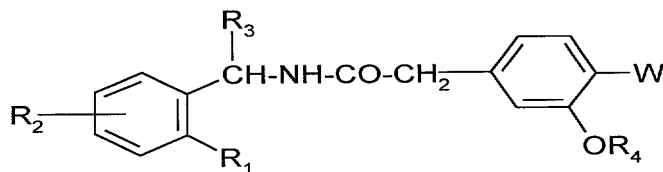
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30

While the present invention has been illustrated with the aid of certain specific embodiments thereof, it will be readily apparent to others skilled in the art that the invention is not limited to these particular embodiments, and that various changes and modifications may be made without departing from the spirit of the invention or the scope of the appended claims.

WE CLAIM:

1. A compound of the formula:



wherein

- $\text{R}_1$  represents an unbranched alkyleneimino group with 4 to 6 carbon atoms optionally mono- or di-(alkyl of 1 to 3 carbon atoms)-substituted;
- $\text{R}_2$  represents a hydrogen or halogen atom or a methyl or methoxy group;
- $\text{R}_3$  represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy, alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain from 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 or 3 carbon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms;
- $\text{R}_4$  represents a hydrogen atom, a methyl, ethyl or allyl group; and
- $\text{W}$  represents a methyl, hydroxymethyl, formyl, carboxyl, alkoxycarbonyl, cyanomethyl, 2-cyanoethyl, 2-cyano-ethenyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonylethenyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group; and

when  $\text{R}_3$  is other than hydrogen and/or the radical  $\text{R}_1$  contains an optically active carbon

atom, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R<sub>1</sub>-position.

2. A compound of claim 1, wherein

R<sub>1</sub> represents a pyrrolidino, piperidino, 4-methyl-piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneiminio group;

R<sub>2</sub> represents a hydrogen, fluorine or chlorine atom;

R<sub>3</sub> represents hydrogen atom, an alkyl group with 1 to 6 carbon atoms, a phenyl, methyl-phenyl, chloro-phenyl, methoxy-phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, tetrahydrofuran-2-yl-methyl, tetrahydropyran-2-yl-methyl, propargyl, hydroxymethyl, ethoxymethyl, acetoxymethyl, propionyloxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl group or an alkenyl group with 3 or 4 carbon atoms;

R<sub>4</sub> represents a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxyl, benzyloxycarbonyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, cyanomethyl, 2-carboxy-ethyl, 2-ethoxycarbonylethyl, 2-cyano-ethyl, 2-carboxy-ethenyl, 2-ethoxycarbonyl-ethenyl or 2-cyano-ethenyl group or an alkoxycarbonyl group with 1 to 4 carbon atoms in the alkoxy part; and

when R<sub>3</sub> is other than hydrogen and/or R<sub>1</sub> represents the 3-methyl-piperidino group, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R<sub>1</sub>-positon.

3. A compound of claim 1, wherein

- R<sub>1</sub>** represents a piperidino group;
- R<sub>2</sub>** represents a hydrogen atom;
- R<sub>3</sub>** represents an alkyl group with 1 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, tetrahydropyran-2-yl-methyl, cyclopropylmethyl or cyclohexylmethyl group;
- R<sub>4</sub>** represents a methyl, ethyl or allyl group; and
- W** represents a carboxyl, methoxycarbonyl, ethoxycarbonyl or cyanomethyl group; and

the enantiomers thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

**4. A compound of claim 1, wherein**

- R<sub>1</sub>** represents a piperidino group;
- R<sub>1</sub>** represents a hydrogen atom;
- R<sub>3</sub>** represents an alkyl group with 3 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, cyclopropylmethyl or cyclohexylmethyl group;
- R<sub>4</sub>** represents a methyl or ethyl group; and
- W** represents a carboxyl group; and

the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

**5. A compound of claim 1, wherein**

- R<sub>1</sub>** represents a piperidino group;
- R<sub>2</sub>** represents a hydrogen atom;
- R<sub>3</sub>** represents an alkyl group with 3 to 6 carbon atoms, a 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group;



R<sub>4</sub> represents a methyl or ethyl group; and

W represents a carboxyl group; and

the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

6. A compound of claim 5, wherein

R<sub>3</sub> represents a n-propyl, n-butyl, isobutyl, sec.butyl, n-pentyl, 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group;

the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid additional salt thereof formed by an inorganic or organic acid with the piperidino function.

7. A compound of claim 5, wherein

R<sub>3</sub> represents a n-propyl, n-butyl, isobutyl, sec.butyl or n-pentyl group; and the enantiomeres thereof or their mixtures; a non- toxic acid additional salt thereof formed by an inorganic or organic acid with the piperidino function.

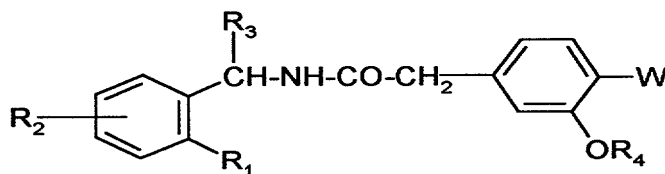
8. The compound of claim 5, which is 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid; the enantiomeres thereof or their mixtures; a nontoxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the piperidino function.

9. The compound of claim 5, which is 2-ethoxy-4-[N(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid; the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the piperidino function.

10. The compound of claim 5, which is form (A) of 2-ethoxy-4[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, recrystallized from acetone/petroleum ether, having a melting point of 90°C -92°C C.
11. The compound of claim 5, which is form (B) of 2-ethoxy-4[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, recrystallized from ethanol/water, having a melting point of 140°C -142°C C.
12. The compound of claim 5, which is form (C) of 2-ethoxy-4[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, recrystallized from methanol, having a melting point of 74°C - 85°C C.
13. The compound of claim 5, which is 2-ethoxy-4-[N-( $\alpha$ -cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid; the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the piperidino function.
14. The (S)-enantiomer or a compound as claimed in any one of the claims 1 to 13; when W is carboxy, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the amino function in the R<sub>1</sub>-position.
15. A hypoglycemic pharmaceutical composition consisting essentially of an inert pharmaceutical carrier and an effective hypoglycemic amount of a compound of claim 1.

# ABSTRACT

Phenylacetic acid benzylamides having the following general structure



wherein the substituents are defined herein, are disclosed, which compounds are hypoglycemic agents.

08945602.100797

**REISSUE APPLICATION DECLARATION BY THE ASSIGNEE**

Docket Number: 5/891

I hereby declare that:

My residence, post office address and citizenship are stated below next to my name.

I represent the following company: Dr. Karl Thomae GmbH

and the title of my position with said company is: Head of Patent Department

The entire title to the patent identified below is vested in said company.

Name of Patentee: Wolfgang Grell et al.

Patent Number: 5,216,167

Date Patent Issued: June 1, 1993

Title of Invention: PHENYLACETIC ACID BENZYLAMIDES

I believe said patentee to be the original, first and sole or joint inventor(s) of the subject matter which is described and claimed in said patent, for which a reissue patent is sought on the invention entitled:

the specification of which

☒ is attached hereto.

☐ was filed on \_\_\_\_\_ as reissue application number \_\_\_\_\_  
and was amended on \_\_\_\_\_.

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below.  
(Check all boxes that apply.)

☐ by reason of a defective specification or drawing, said defects being described below.

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent, said excess or insufficiency in the claims being specified below.

☐ by reason of other errors, described below.

The errors relied upon in the above statement, and how the errors occurred, are as follows:

Assignee Dr. Karl Thomae GmbH, also the owner of U.S. Patents 4,873,080 and 4,863,724 (issued October 10, 1989 and September 5, 1989, respectively), believes that the term of U.S. Pat. 5,216,167 subsequent to September 5, 2006 should be disclaimed.

The errors described above arose without any deceptive intention on the part of the applicant.

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the patent and Trademark Office connected therewith.

Name(s)

Registration No.:

Alan R. Stempel  
Mary-Ellen M. Devlin

29,881  
27,928

Correspondence Address: Direct all communications about the application to:


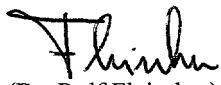
Customer Number

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**OR**

Firm or Individual Name	Boehringer Ingelheim Corporation				
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of person signing (given name, family name) Dr. Karl Thomae GmbH	Full name of person signing (given name, family name) Dr. Karl Thomae GmbH
Signature ppa.  (Dr. Manfred Reiffen)	Signature ppa.  (Dr. Rolf Fleischer)
Date 12. September 1997	Date 12. September 1997
Residence: D-88397 Biberach	Residence: D-88397 Biberach
Citizenship: german	Citizenship: german
Post Office Address Birkendorfer Straße 65 D-88397 Biberach	Post Office Address Birkendorfer Straße 65 D-88397 Biberach

**REISSUE APPLICATION BY THE ASSIGNEE,  
OFFER TO SURRENDER PATENT**

Docket No.: 5/891

This is part of the application for a reissue patent based on the original patent identified below.

Name of Patentee: Wolfgang Grell et al.

Patent Number: 5,216,167

Date Patent Issued: June 1, 1993

Title of Invention: PHENYLACETIC ACID BENZYLAMIDES

I am the assignee of the entire interest in said original patent.

I offer to surrender said original patent.

Filed herein is:

- ☒ a certified copy of an abstract of title.
- ☐ an order for a title report. The fee for this order is \$\_\_\_\_(37 CFR 1.19(b)(4)).
- ☐ A check in the amount of the fee is enclosed.
- ☐ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required or credit any overpayment of Deposit Account Number 02-2955. I have enclosed a duplicate copy of this sheet.

Name of assignee: Dr. Karl Thomae GmbH

Signature of person signing for assignee

Date:

*Mary-Ellen M. Devlin*

Typed or printed name and title of person signing for assignee: Mary-Ellen M. Devlin, Patent Attorney